

<b>L Number</b>	<b>Hits</b>	<b>Search Text</b>	<b>DB</b>	<b>Time stamp</b>
<b>1</b>	<b>2</b>	<b>"bacteria-to-bacteria"</b>	<b>USPAT; US-PGPUB; EPO; JPO; DERWENT</b>	<b>2003/02/19 17:13</b>
-	<b>22</b>	<b>plasmid same bacteria same gene same transfer\$ same prevent\$</b>	<b>USPAT; US-PGPUB; EPO; JPO; DERWENT</b>	<b>2003/02/19 14:22</b>
-	<b>1</b>	<b>(plasmid same bacteria same gene same transfer\$ same prevent\$) and taurolidine</b>	<b>USPAT; US-PGPUB; EPO; JPO; DERWENT</b>	<b>2003/02/19 14:34</b>
-	<b>1</b>	<b>"bacteria-to-bacteria transfer"</b>	<b>USPAT; US-PGPUB; EPO; JPO; DERWENT</b>	<b>2003/02/19 17:13</b>

=> file caplus wpids biosis medline embase

FILE 'CAPLUS' ENTERED AT 17:22:41 ON 19 FEB 2003  
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FILE 'WPIDS' ENTERED AT 17:22:41 ON 19 FEB 2003  
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FILE 'MEDLINE' ENTERED AT 17:22:41 ON 19 FEB 2003

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=> d his

(FILE 'HOME' ENTERED AT 17:22:04 ON 19 FEB 2003)

FILE 'CAPLUS, WPIDS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 17:22:41 ON 19 FEB 2003

L1 85846 "BACTERIA-TO-BACTERIA"  
L2 384 L1 AND PLASMID AND GENES AND DNA  
L3 7 L1 AND TAUROLIDINE  
L4 202 L1(P) (PLASMID OR DNA)  
L5 29 L4(P) (PREVENT? OR INHIBIT?)

=> "bacteria-to-bacteria"

L1 85846 "BACTERIA-TO-BACTERIA"

=> l1 and plasmid and genes and DNA

L2 384 L1 AND PLASMID AND GENES AND DNA

=> l1 and taurolidine

L3 7 L1 AND TAUROLIDINE

=> d l3 1-7 ibib ab

L3 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2002:558999 BIOSIS  
DOCUMENT NUMBER: PREV200200558999  
TITLE: Efficacy and tolerance of selected antiseptic substances  
in respect of suitability for use on the eye.  
AUTHOR(S): Kramer, A. (1); Rudolph, P.  
CORPORATE SOURCE: (1) Institute of Hygiene and Environmental Medicine, Ernst  
Moritz Arndt University, Hainstrasse 26, D-17487,  
Greifswald: kramer@uni-greifswald.de Germany  
SOURCE: Kramer, A. [Editor]; Behrens-Baumann, W. [Editor].  
Developments in Ophthalmology, (2002) Vol. 33, pp.  
117-144.  
Developments in Ophthalmology. Antiseptic prophylaxis and  
therapy in ocular infections: Principles, clinical  
practice and infection control. print.  
Publisher: S. Karger AG CH-4009, Basel, Switzerland.

ISSN: 0250-3751. ISBN: 3-8055-7316-2 (cloth).

DOCUMENT TYPE: Book  
 LANGUAGE: English

L3 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 ACCESSION NUMBER: 2000:16921 BIOSIS  
 DOCUMENT NUMBER: PREV200000016921  
 TITLE: Local treatment of generalised peritonitis in rats;  
 Effects on bacteria, endotoxin and mortality.

AUTHOR(S): Rosman, Camiel (1); Westerveld, Gert J.; Kooi, Kor;  
 Bleichrodt, Robert P.

CORPORATE SOURCE: (1) Department of Surgery, University Hospital Groningen,  
 NL-9700 RB, Groningen Netherlands

SOURCE: European Journal of Surgery, (Nov., 1999) Vol. 165, No.  
 11,  
 pp. 1072-1079.  
 ISSN: 1102-4151.

DOCUMENT TYPE: Article  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

AB Objective: To assess the effect of debridement, intraoperative lavage  
 with saline, and additional instillation of **taurolidine** or  
 imipenem/cilastatin in rats with faecal peritonitis. Design: Laboratory  
 study. Setting: University hospital, The Netherlands. Material: 60 male  
 Wistar rats. Interventions: Rats were given an intraperitoneal injection  
 of a faecal suspension containing Escherichia coli and Bacteroides  
 fragilis. Six groups of 10: sham operation, debridement, debridement with  
 saline lavage, debridement with saline lavage with intraperitoneal  
 instillation of saline or **taurolidine**, or imipenem/cilastatin,  
 were studied. Main outcome measures: Bacterial growth and endotoxin  
 concentration in abdominal exudate and plasma, abscess formation, and  
 mortality. Results: Debridement temporarily reduced bacterial growth and  
 the concentration of endotoxin in abdominal exudate, and delayed  
 mortality. Lavage with saline further reduced bacterial growth and the  
 endotoxin concentration. It also reduced the plasma endotoxin  
 concentration, and mortality. Additional instillation of  
**taurolidine** did not reduce bacterial growth, but did initially  
 reduce the endotoxin concentration in abdominal exudate and plasma.  
 Instillation of imipenem/cilastatin, after debridement and lavage,  
 significantly reduced all variables measured. Conclusion: In rats with  
 faecal peritonitis, debridement, lavage with saline, and additional  
 instillation of imipenem/cilastatin, all have cumulatively reducing  
 effect on bacterial growth, endotoxin concentrations, abscess formation, and  
 mortality. Instillation of **taurolidine** reduces only the amount  
 of endotoxin.

L3 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 ACCESSION NUMBER: 1997:402244 BIOSIS  
 DOCUMENT NUMBER: PREV199799708447  
 TITLE: Spectrum of pathogens and resistance in peritonitis.  
 AUTHOR(S): Focht, J. (1); Noesner, K.  
 CORPORATE SOURCE: (1) Biosci., Inst. Laboruntersuchungen, Zum  
 Schuermansgraben 30, D-47441 Moers Germany  
 SOURCE: Langenbecks Archiv fuer Chirurgie, (1997) Vol. 382, No. 4  
 SUPPL. 1, pp. S1-S4.  
 ISSN: 0023-8236.

DOCUMENT TYPE: Article

LANGUAGE: German

SUMMARY LANGUAGE: German; English

AB Severe intra-abdominal infection is associated with a high mortality rate.

In addition to risk factors in the patients, the causal pathogens and the selection of appropriate therapeutic procedures play an essential part in the course of these conditions. In the majority of intra-abdominal infections mixed aerobic/anaerobic infections, mostly with some involvement of enterobacteria and also of enterococci and staphylococci can be demonstrated. In addition to surgical intervention a calculated antimicrobial initial treatment of intra-abdominal infections with an antibiotic with an adequate effect to combat the pathogen concerned can contribute to improving the patient's prognosis. A calculated antibiotic treatment can only be effectively and reliably carried through if the frequency of the pathogen and the resistance situation are known. Retrospective evaluations of data on the sensitivity and frequency of pathogens from a defined group of subjects allow conclusions on the epidemiological situation in a particular catchment area or in a medical sector and thus make it possible to calculate the appropriate therapy for infections. In 1996 a total of 2,779 bacterial isolates from the intra-abdominal infection sector were examined: 935 Enterobacteriaceae,

83

nonfermenters, 177 Staphylococcus spp., 211 Enterococcus spp., 39 Streptococcus spp., and 1334 different anaerobic bacteria. Fresh clinical isolates were available for all pathogens tested. The most frequent gram-negative pathogen was *E. coli* (60%) and the most frequent gram-positive pathogen, *E. faecalis* (44%); the most frequent anaerobic pathogen was *B. fragilis* (39%). Tauroldine had the lowest resistance

rate

against gram-negative and anaerobic pathogens. Teicoplanin had the highest activity against gram-positive pathogens.

L3 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:510366 BIOSIS

DOCUMENT NUMBER: PREV199699232722

TITLE: Effect of intraperitoneal antimicrobials on the concentration of bacteria, endotoxin, and tumor necrosis factor in abdominal fluid and plasma in rats.

AUTHOR(S): Rosman, C. (1); Westerveld, G. J.; Van Oeveren, W.; Kooi, K.; Bleichrodt, R. P.

CORPORATE SOURCE: (1) Dep. Surgery, Medisch Spectrum Twente, PO Box 50.000, NL-7500 KA Enschede Netherlands

SOURCE: European Surgical Research, (1996) Vol. 28, No. 5, pp. 351-360.  
ISSN: 0014-312X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The efficacy of intraperitoneal instillation of antimicrobial agents in eliminating the bacterial contaminant in patients with generalized peritonitis remains controversial. We determined the effect of intraperitoneal instillation of **tauroldine** or imipenem on mortality, and on the concentration of bacteria, endotoxin, and tumor necrosis factor (TNF) in rats with intraperitoneally injected bacteria. Thirty rats were inoculated intraperitoneally with two enteric bacterial strains, followed by either **tauroldine**, saline, or imipenem. Abdominal fluid and blood were analyzed at different time intervals. The survival rate was highest in the imipenem group ( $p < 0.05$ ). The bacterial concentration in abdominal fluid in the **tauroldine** and imipenem

group was lower than in the saline group (p lt 0.005), but the concentration in the imipenem group was lowest (p lt 0.005). The endotoxin concentration in abdominal fluid and plasma in the **taurolidine** group was lower than in the other two groups (p lt 0.05). The TNF concentration in abdominal fluid and plasma in the **taurolidine** group was lower than in the saline group (p lt 0.05), whereas the concentration in the imipenem group was higher (p lt 0.005). We conclude that topically applied **taurolidine** in rats with intraperitoneally injected bacteria may have a weak antibacterial effect, and lowered concentrations of endotoxin and TNF. Topically applied imipenem had a profound bactericidal activity but induced endotoxin and TNF release.

L3 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 1995:346923 BIOSIS  
DOCUMENT NUMBER: PREV199598361223  
TITLE: Effect of the antiendotoxic agent, **taurolidine**, in the treatment of sepsis syndrome: A placebo-controlled, double-blind trial.  
AUTHOR(S): Willatts, Sheila M. (1); Radford, Sheila; Leitermann, Marie  
CORPORATE SOURCE: (1) Intensive Therapy Unit, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW UK  
SOURCE: Critical Care Medicine, (1995) Vol. 23, No. 6, pp. 1033-1039.  
ISSN: 0090-3493.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
AB Objective: To assess the benefit gained from administration of the antiendotoxic drug, **taurolidine**, on outcome in critically ill patients with sepsis syndrome. Design: A prospective, randomized, double-blind trial. Setting. The general intensive therapy unit in a university teaching hospital. Patients: One hundred patients admitted with sepsis syndrome over a 2-yr period. Interventions: Patients were randomized to receive the amino-acid derivative, **taurolidine**, or an identically presented placebo. Measurements and Main Results: Acute Physiology and Chronic Health Evaluation II (APACHE II), sepsis, and organ failure scores were measured daily. Blood for culture and endotoxin assay (using the limulus amoebocyte lysate assay) was sampled every 12 hrs for up to 5 days. Hemodynamic variables were recorded every 4 hrs. Forty-nine patients received **taurolidine** and 51 patients received placebo. There was no difference in APACHE II score, Sepsis Score, or presence of infections between the groups. The frequency of Gram-negative bacteremia was low at 12%. There was no difference in endotoxin activity, clinical or bacteriologic outcome, resolution of organ failure, or mortality rate between groups. Predicted risk of death for patients receiving **taurolidine** was 45%, and the actual mortality rate was 44%. In the group that received placebo, the predicted mortality rate was 38% and the actual mortality rate was 39%. Conclusion: **Taurolidine** had no beneficial therapeutic effect on the outcome of patients admitted to the intensive therapy unit with sepsis syndrome, using clinical, bacteriologic outcomes, progression of endotoxemia, resolution of organ failure, and 28-day mortality rate as end points.

L3 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1994:13881 BIOSIS  
DOCUMENT NUMBER: PREV199497026881  
TITLE: **Taurolidine**, anti-lipopolysaccharide (LPS) agent  
with immunostimulatory properties.  
AUTHOR(S): Watson, R. William G. (1); Redmond, H. Paul; McCarthy,  
Julie; Croke, T. David; Burke, Paul; Bouchier-Hayes, David  
CORPORATE SOURCE: (1) Dep. Surg., Beaumont Hosp., Dublin Ireland  
SOURCE: Surgical Forum, (1993) Vol. 44, No. 0, pp. 90-91.  
ISSN: 0071-8041.  
DOCUMENT TYPE: Article  
LANGUAGE: English

L3 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 1993:25354 BIOSIS  
DOCUMENT NUMBER: PREV199395013554  
TITLE: In vitro activity of **taurolidine**,  
chlorophenol-camphor-menthol and chlorhexidine against  
oral

pathogenic microorganisms.  
AUTHOR(S): Zimmermann, M. (1); Preac-Mursic, V.  
CORPORATE SOURCE: (1) Klin. Poliklin. Kieferchirurgie, Univ. Muenchen,  
Lindwurmstr. 2a, W-8000 Muenchen 2 Germany  
SOURCE: Arzneimittel-Forschung, (1992) Vol. 42, No. 9, pp.  
1157-1159.  
ISSN: 0004-4172.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English; German

AB The antimicrobial activity of **taurolidine** (Taurolin, CAS  
19388-87-5), a synthetic broad-spectrum antimicrobial agent and  
anti-toxin, and two conventional antiseptics,  
chlorophenol-camphor-menthol  
(CCM) and chlorhexidine digluconate (CHX) were compared using the serial  
dilution test on 10 potential oral pathogenic bacterial species. The  
minimum inhibitory and minimum bactericidal concentrations were lowest  
for  
CHX (MIC 0.03-0.12 mg/ml), followed by **taurolidine** (MIC 0.12-0.5  
mg/ml) and CCM (MIC 0.5-2.0 mg/ml). However, if both bacterial efficacy  
and cytotoxicity are considered, only **taurolidine** achieves  
extensive bactericidal activity with tissue tolerability.

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FILE 'CAPLUS, WPIDS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 17:22:41 ON 19  
FEB 2003

L1 85846 "BACTERIA-TO-BACTERIA"  
L2 384 L1 AND PLASMID AND GENES AND DNA  
L3 7 L1 AND TAUROLIDINE

=> l1(p) (plasmid or DNA)

L4 202 L1(P) (PLASMID OR DNA)

=> l4(p) (prevent? or inhibit?)

L5 29 L4(P) (PREVENT? OR INHIBIT?)

=> d l5 1-29 ibib ab

L5 ANSWER 1 OF 29 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:740747 CAPLUS

DOCUMENT NUMBER: 138:12965

TITLE: Review article: the role of the gut flora in health and disease, and its modification as therapy

AUTHOR(S): Hart, A. L.; Stagg, A. J.; Frame, M.; Graffner, H.; Glise, H.; Falk, P.; Kamm, M. A.

CORPORATE SOURCE: St Mark's Hospital, Harrow, Middlesex, UK

SOURCE: Alimentary Pharmacology and Therapeutics (2002), 16(8), 1383-1393

CODEN: APTHEN; ISSN: 0269-2813

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The gut flora is a vast interior ecosystem whose nature is only

beginning to be unravelled, due to the emergence of sophisticated mol. tools. Techniques such as 16S rRNA anal., polymerase chain reaction amplification and the use of **DNA** microarrays now facilitate rapid identification and characterization of species resistant to conventional culture and possibly unknown species. Life-long cross-talk between the host and the gut flora detcs. whether health is maintained or disease intervenes. An understanding of these **bacteria-bacteria** and **bacteria**-host immune and epithelial cell interactions is likely to lead to a greater insight into disease pathogenesis. Studies of single organism-epithelial interactions have revealed the large range of metabolic processes that gut bacteria may influence. In inflammatory bowel diseases, bacteria drive the inflammatory process, and genetic predisposition to disease identified to date, such as the recently described NOD2/CARD15 gene variants may relate to altered bacterial recognition. Extra-intestinal disorders, such as atopy and arthritis, may also have an altered gut milieu as their basis. Clin. evidence is emerging that the modification of this internal environment, using either antibiotics or probiotic bacteria, is

beneficial

in **preventing** and treating disease. This natural and apparently safe approach holds great appeal.

REFERENCE COUNT: 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L5 ANSWER 2 OF 29 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:90224 CAPLUS

DOCUMENT NUMBER: 136:129913

TITLE: Mutational analysis in isolation of regulated virulence determinants of bacterial pathogens and the rtxA and enhC genes from Legionella pneumophila

INVENTOR(S): Cirillo, Jeffrey D.

PATENT ASSIGNEE(S): The Board of Regents of the University of Nebraska, USA

SOURCE: PCT Int. Appl., 131 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2002008418 A2 20020131 WO 2001-US23306 20010724  
WO 2002008418 A3 20020613

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,  
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,  
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-628871 A 20000724

AB The present invention relates to novel methods for isolation and identification of virulence determinants from bacterial pathogens. The present invention also relates to novel genes of the Legionella pneumophila bacteria, and methods of detection of Legionella pneumophila bacteria in samples. The present invention relates to novel methods for isolation and identification of virulence determinants from bacterial pathogens. A pool of bacterial mutants with enhanced virulence phenotype is obtained, and the **DNA** responsible as a factor for the enhanced virulence is located. Random mutations are inserted into the **DNA**, the **DNA** transferred into wild-type **bacteria**, and **bacteria** that no longer express the enhanced virulence are selected in order to identify an active site of the **DNA** necessary to confer enhanced virulence. The present invention also more specifically relates to novel rtxA and enhC genes of the Legionella pneumophila bacteria. Gene rtxA affects bacterial adherence to monocytes and epithelial cells, is involved in cytotoxicity and pore formation by

L. pneumophila, and affects the bacterial virulence. These genes allow for the detection and quantitation of L. pneumophila and thus diagnosis of Legionnaires' disease, as well as for the design of **inhibitors** of the protein products of the genes.

L5 ANSWER 3 OF 29 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12666 CAPLUS

DOCUMENT NUMBER: 134:96206

TITLE: General method for isolation of regulated virulence determinants from bacterial pathogens and the rtxA

and

enhC genes from Legionella pneumophila

INVENTOR(S): Cirillo, Jeffrey D.

PATENT ASSIGNEE(S): The Board of Regents of the University of Nebraska, USA

SOURCE: PCT Int. Appl., 105 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000877	A2	20010104	WO 2000-US17743	20000627
WO 2001000877	A3	20020510		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,



ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 US 2002086304 A1 20020704 US 2001-881901 20010615  
 US 2002086981 A1 20020704 US 2001-882583 20010615  
 PRIORITY APPLN. INFO.: US 1999-141717P P 19990630  
 US 2000-604561 A3 20000627

AB The present invention relates to novel methods for isolation and  
 identification of virulence determinants from bacterial pathogens. A  
 pool of bacterial mutants with enhanced virulence phenotype is obtained, and  
 the **DNA** responsible as a factor for the enhanced virulence is  
 located. Random mutations are inserted into the **DNA**, the  
**DNA** transferred into wild-type **bacteria**, and  
**bacteria** that no longer express the enhanced virulence are  
 selected in order to identify an active site of the **DNA**  
 necessary to confer enhanced virulence. The present invention also more  
 specifically relates to novel *rtxA* and *enhC* genes of the *Legionella*  
*pneumophila* bacteria. Gene *rtxA* affects bacterial adherence to monocytes  
 and epithelial cells, is involved in cytotoxicity and pore formation by  
 L. *pneumophila*, and affects the bacterial virulence. These genes allow for  
 the detection and quantitation of *L. pneumophila* and thus diagnosis of  
 Legionnaires' disease, as well as for the design of **inhibitors**  
 of the protein products of the genes.

L5 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:261712 CAPLUS  
 DOCUMENT NUMBER: 124:308780  
 TITLE: Update on gene amplification kits for medical  
 bacteriological laboratory  
 AUTHOR(S): Stoessel, P.; Jaulhac, B.  
 CORPORATE SOURCE: Faculte de Medecine, Institut de Bacteriologie de la,  
 Strasbourg, 67000, Fr.  
 SOURCE: Spectra Biologie (1996), 15(76), 37-42  
 CODEN: SPEBEQ; ISSN: 0295-1967  
 PUBLISHER: Spectra Biologie  
 DOCUMENT TYPE: Journal  
 LANGUAGE: French

AB Recent developments in mol. biol. allow detection of fastidious  
**bacteria** or **bacteria** requiring a long culture time. Two  
 methods exist, **DNA** hybridization and nucleic acid amplification.  
**DNA** hybridization is specific and rapid but is not sensitive  
 enough to be used with low inoculums. However, with the amplification  
 techniques, the sensitivity is increased. The purpose of the present  
 article is to evaluate the nucleic acid amplification tests which are  
 com. available in 1995 or will be available. Two types of tests exist:  
 non-isothermic tests using polymerase chain reaction or ligase chain  
 reaction requiring a thermocycler to automate thermal variation, and  
 isothermic tests (transcription mediated amplification, nucleic acid  
 based amplification, strand displacement amplification) which only require an  
 incubator. Kits currently available for bacteriol. applications are for  
*Chlamydia trachomatis* and *mycobacteria*. These kits have a sensitivity of  
 greater than 90% and a specificity approaching 100%. However, there are  
 tech. limitations for these methods such as the **inhibitors** of  
 enzyme activity (leading to false neg. results) and contamination  
 (leading

to false pos. results).

L5 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1987:135100 CAPLUS

DOCUMENT NUMBER: 106:135100

TITLE: Antibacterial activity and mechanism of action of 3'-azido-3'-deoxythymidine (BW A509U)

AUTHOR(S): Elwell, Lynn P.; Ferone, Robert; Freeman, G. Andrew; Fyfe, James A.; Hill, John A.; Ray, Paul H.;

Richards, Cynthia A.; Singer, Sara C.; Knick, Victoria B.; et al.

CORPORATE SOURCE: Dep. Microbiol., Wellcome Res. Lab., Research Triangle

Park, NC, 27709, USA

SOURCE: Antimicrobial Agents and Chemotherapy (1987), 31(2), 274-80

CODEN: AMACQ; ISSN: 0066-4804

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The thymidine analog 3'-azido-3'-deoxythymidine (AZT) had potent bactericidal activity against many members of the family Enterobacteriaceae, including strains of Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Shigella flexneri, and Enterobacter aerogenes. AZT also had bactericidal activity against Vibrio cholerae

and the fish pathogen V. anguillarum. AZT had no activity against Pseudomonas

aeruginosa, gram-pos. **bacteria**, anaerobic **bacteria**, Mycobacterium tuberculosis, nontuberculosis mycobacteria, or most fungal pathogens. Several lines of evidence indicated that AZT must be activated

to the nucleotide level to **inhibit** cellular metab.: (1) AZT was a substrate for E. coli thymidine kinase, (2) spontaneously arising AZT-resistant mutants of E. coli ML-30 and S. typhimurium were deficient in thymidine kinase, and (3) intact E. coli ML-30 cells converted [3H]AZT to its mono-, di-, and triphosphate metabolites. Of the phosphorylated metabolites, AZT-5'-triphosphate was the most potent **inhibitor** of replicative **DNA** synthesis in toluene-permeabilized E. coli pol A mutant cells. AZT-treated E. coli cultures grown in minimal medium contained highly elongated cells consistent with the **inhibition** of **DNA** synthesis. AZT-triphosphate was a specific **DNA** chain terminator in the in vitro **DNA** polymn. reaction catalyzed by the Klenow fragment of E. coli **DNA** polymerase I. Thus, **DNA** chain termination may explain the lethal properties of this compd. against susceptible microorganisms.

L5 ANSWER 6 OF 29 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2002-590500 [63] WPIDS

DOC. NO. CPI: C2002-166963

TITLE: New DNA methyltransferase inhibitors useful in the treatment of bacterial infections e.g. bacterial meningitis.

DERWENT CLASS: B03

INVENTOR(S): BABOVAL, J; BAKER, S J; BENKOVIC, S J; SCOTT, C P; SHAPIRO, L; SHIER, V K; WAHNON, D C; WALL, M

PATENT ASSIGNEE(S): (PENN-N) PENN STATE RES FOUND

COUNTRY COUNT: 96

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002044184	A2	20020606	(200263)*	EN	35
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2002039407	A	20020611	(200264)		

# APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002044184	A2	WO 2001-US45129	20011129
AU 2002039407	A	AU 2002-39407	20011129

# FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002039407	A Based on	WO 200244184

PRIORITY APPLN. INFO: US 2000-250202P 20001130

AB WO 200244184 A UPAB: 20021031

NOVELTY - DNA methyltransferase inhibitors (I) are new.

DETAILED DESCRIPTION - DNA methyltransferase inhibitors of formula (I) and their salts are new.

A = N, O or S;

W = Cp;

p = 0-1;

has Ra-Re = cycloalkyl, cycloalkyl alkoxy (where the cycloalkyl group

3-7 members and up to 2 atoms are optionally substituted by heteroatoms selected from S, O or N), lower alkyl, optionally substituted aryl (all optionally substituted by halo, lower alkyl, lower alkoxy, optionally substituted aryl, nitro, nitroso, aldehyde, carboxylic acid, amide, ester or sulfate), H, halo, nitro, nitroso, lower alkoxy or lower alkoxyalkyl; and

Ra-Re = connected by optionally substituted aromatic, aliphatic, heteroaromatic, heteroaliphatic rings;

Ar1, Ar2 = optionally substituted aryl (substituted by at least one position by Ra);

Ar1+Ar2 = tricyclic scaffold of formula (i);

X = C=O, CHOH, (CH2)n, CH=CH, NRf, O, SOn (having several positions with cycloalkyl, cycloalkyl alkoxy (in which cycloalkyl has 3-7 members and in which up to two cycloalkyl members are optionally heteroatoms selected from S, O or N), halo, nitro, nitroso, lower alkyl, optionally substituted aryl, lower alkoxy or lower alkoxyalkyl; and

a'-d' = single or double bond;

provided that:

(i) when A is O or S, Ra is absent;

(ii) when p is 0, Rd is absent; and

(iii) when A is S or O, a' is single bond and when A is N, a' is a double bond.

INDEPENDENT CLAIMS are also included for:

(1) a combinatorial library comprising multiplicity of (I); and

(2) a packaged pharmaceutical composition comprising the composition in a container and instructions for using the composition in the treatment

of a patient suffering from a disease associated with infection with a pathogenic bacterium.

ACTIVITY - Antibacterial; Antiinflammatory; Immunosuppressive; Antirheumatic; Antipyretic.

MECHANISM OF ACTION - DNA methyltransferase inhibitor; Cellular process modulator; Cell growth inhibitor.

In a cell growth assay using *Bacillus subtilis*, di-(para-chlorophenyl)borinic acid 8-hydroxyquinaldine ester (Ia) inhibited cell growth with an IC50 of 24 micro M.

USE - In the treatment of disease associated with infection with pathogenic bacteria such as *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Clostridium perfringens*, *Clostridium botulinum*, *Clostridium tetani*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Escherichia coli*, *Yersinia pestis*, *Hemophilus influenzae*, *Helicobacter pylori*, *Campylobacter fetus*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Treponema pallidum*, *Actinomyces israelii*, *Rickettsia prowazekii*, *Rickettsia rickettsii*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Brucella abortus* and *Agrobacterium tumefaciens* expressing adenine DNA methyltransferase (all claimed). As antibiotic in the treatment of actinomycosis, anthrax, bacterial dysentery, botulism, brucellosis, cellulitis, cholera, conjunctivitis, cystitis, diphtheria, bacterial endocarditis, epiglottitis, gastroenteritis, glanders, gonorrhea, Legionnaire's disease, leptospirosis, bacterial meningitis, plague, bacterial pneumonia, puerperal sepsis, rheumatic fever, Rocky Mountain spotted fever, scarlet fever, streptococcal pharyngitis, syphilis, tetanus, tularemia, typhoid fever, typhus and pertussis.

ADVANTAGE - (I) Exhibits DNA methyltransferase inhibitory activity. (I) Exhibits low cytosine-specific DNA methyltransferase activity. (I) Is bacterial cell specific and has little antibiotic activity against mammalian.

Dwg.0/0

L5 ANSWER 7 OF 29 WPIDS (C) 2003 THOMSON DERWENT  
ACCESSION NUMBER: 2002-557291 [59] WPIDS  
CROSS REFERENCE: 2000-532863 [48]; 2002-598710 [64]; 2002-635659 [68];  
2002-635674 [68]; 2002-690113 [74]  
DOC. NO. CPI: C2002-158052  
TITLE: Reducing bacterial virulence using an agent that alters  
the bacteria's native level of DNA methyltransferase  
activity.  
DERWENT CLASS: B04 D16  
INVENTOR(S): HEITHOFF, D M; LOW, D A; MAHAN, M J; SINSHEIMER, R L  
PATENT ASSIGNEE(S): (HEIT-I) HEITHOFF D M; (LOWD-I) LOW D A; (MAHA-I) MAHAN  
M  
J; (SINS-I) SINSHEIMER R L  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002077272	A1	20020620	(200259)*		35

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002077272	A1	Provisional	US 1999-183043P 19990202
		Provisional	US 1999-198250P 19990505

CIP of	US 2000-495614	20000201
CIP of	US 2000-612116	20000707
	US 2001-927885	20010809

PRIORITY APPLN. INFO: US 2001-927885 20010809; US 1999-183043P  
 19990202; US 1999-198250P 19990505; US  
 2000-495614 20000201; US 2000-612116 20000707

AB US2002077272 A UPAB: 20021120

NOVELTY - Reducing bacterial virulence comprising contacting bacteria  
 with

an agent that alters the bacteria's native level of **DNA**  
 methyltransferase (Dam) activity thereby altering the bacteria's native  
 level of methylation of adenine in a GATC tetranucleotide of the  
 bacteria,  
 and thereby **inhibiting** virulence of the bacteria.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the  
 following:

(1) reducing pathogenicity of a pathogenic bacteria, comprising  
 administering an agent that alters a pathogenic bacteria's native Dam  
 activity thereby altering the bacteria's native **DNA** methylation  
 activity to an extent that the bacteria's pathogenicity is reduced;

(2) treating a bacterial infection, comprising administering to a  
 subject infected with a pathogenic bacteria a therapeutically effective  
 amount of a composition comprising a pharmaceutically acceptable carrier  
 and an agent that alters the bacteria's native level of Dam activity;

(3) treating bacterial infection comprising administering an agent  
 that reduces the level or activity of a **DNA** methyltransferase  
 thus reducing methylation of adenine in a GATC tetranucleotide in the  
 bacteria, **inhibiting** the virulence of the bacteria;

(4) a composition for controlling bacterial pathogenicity,  
 comprising

a carrier, and a compound that alters native Dam activity; and

(5) an attenuated strain of a **bacteria**, the  
**bacteria** comprising altered Dam activity.

ACTIVITY - Antibacterial. No suitable biodata provided.

MECHANISM OF ACTION - **DNA** methyltransferase activity  
 modulator.

USE - The methods are useful for reducing bacterial virulence;  
 reducing pathogenicity of a pathogenic bacteria, comprising administering  
 an agent that alters a pathogenic bacteria's native Dam activity thereby  
 altering the bacteria's native **DNA** methylation activity to an  
 extent that the bacteria's pathogenicity is reduced; and treating a  
 bacterial infection, the bacteria are e.g. Haemophilus, salmonella,  
 Escherichia, and Vibrio (claimed).

Dwg.0/9

L5 ANSWER 8 OF 29 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2001-292928 [31] WPIDS

DOC. NO. CPI: C2001-089883

TITLE: New enolase gene from coryneform bacteria, used to  
 prepare transformants with increased synthesis of amino  
 acids, particularly lysine.

DERWENT CLASS: B05 D16 E16

INVENTOR(S): BATHE, B; HERMANN, T; KALINOWSKI, J; MOCKEL, B;  
 PFEFFERLE, W; PUHLER, A; MOECKEL, B; PUEHLER, A

PATENT ASSIGNEE(S): (DEGS) DEGUSSA-HUELS AG; (BATH-I) BATHE B; (HERM-I)  
 HERMANN T; (KALI-I) KALINOWSKI J; (MOCK-I) MOCKEL B;  
 (PFEF-I) PFEFFERLE W; (PUHL-I) PUHLER A

COUNTRY COUNT: 35

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1090998	A1	20010411	(200131)*	GE	25
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
DE 19947791	A1	20010412	(200131)		
AU 2000061359	A	20010412	(200132)		
CA 2319716	A1	20010405	(200133)	EN	
BR 2000004643	A	20010612	(200137)		
CN 1290750	A	20010411	(200140)		
JP 2001161380	A	20010619	(200140)		13
ZA 2000005409	A	20010627	(200140)		34
SK 2000001458	A3	20010710	(200157)		
KR 2001050840	A	20010625	(200172)		
US 2002082403	A1	20020627	(200245)		
HU 2000003893	A1	20020930	(200272)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1090998	A1	EP 2000-121158	20000929
DE 19947791	A1	DE 1999-19947791	19991005
AU 2000061359	A	AU 2000-61359	20000928
CA 2319716	A1	CA 2000-2319716	20001004
BR 2000004643	A	BR 2000-4643	20001004
CN 1290750	A	CN 2000-129571	20000927
JP 2001161380	A	JP 2000-305110	20001004
ZA 2000005409	A	ZA 2000-5409	20001004
SK 2000001458	A3	SK 2000-1458	20000929
KR 2001050840	A	KR 2000-58213	20001004
US 2002082403	A1 CIP of	US 1999-455779	19991207
		US 2001-860768	20010521
HU 2000003893	A1	HU 2000-3893	20001004

PRIORITY APPLN. INFO: DE 1999-19947791 19991005

AB EP 1090998 A UPAB: 20010615

NOVELTY - An isolated nucleic acid (I) from coryneform bacteria encoding a

polypeptide at least 70 % identical with a 425 residue amino acid sequence

(S2), or having a complementary nucleotide sequence, or at least 15 consecutive bases of it, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for fermentative production of L-amino acids, especially L-lysine, by fermenting a lysine-producing coryneform in which the eno gene has been amplified, and isolating amino acids that have accumulated in the medium or cells.

USE - (I), which encodes an enolase, is used to transform coryneforms

for production of L-amino acids, specifically lysine which is used in medicine and particularly as animal feed supplement (claimed). It may also

be used as probes and primers for isolating related sequences.

ADVANTAGE - Overexpression of (I) improves production of amino acids, especially of L-lysine.

Dwg.0/2

L5 ANSWER 9 OF 29 WPIDS (C) 2003 THOMSON DERWENT  
ACCESSION NUMBER: 2001-202774 [20] WPIDS  
DOC. NO. NON-CPI: N2001-144679  
DOC. NO. CPI: C2001-060211  
TITLE: Enzymes which operate in the alternative isoprenoid  
pathway downstream from 2C-methyl-D-erythritol-4-  
phosphate, useful for screening a chemical library for  
inhibitors of the biosynthesis of isoprenoids.  
DERWENT CLASS: C06 D16 S03  
INVENTOR(S): BACHER, A; EISENREICH, W; FELLERMEIER, M; FISCHER, M;  
HECHT, S; HERZ, S; KIS, K; LUETTGEN, H; ROHDICH, F;  
SAGNER, S; SCHUHR, C A; WUNGSINTAWEEKUL, J; ZENK, M  
PATENT ASSIGNEE(S): (BACH-I) BACHER A; (ZENK-I) ZENK M; (ZENK-I) ZENK M H  
COUNTRY COUNT: 93  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001011055	A1	20010215	(200120)*	EN	180
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
DE 10020996	A1	20010322	(200124)		
AU 2000062803	A	20010305	(200130)		
EP 1198575	A1	20020424	(200235)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001011055	A1	WO 2000-EP7548	20000803
DE 10020996	A1	DE 2000-10020996	20000428
AU 2000062803	A	AU 2000-62803	20000803
EP 1198575	A1	EP 2000-949452	20000803
		WO 2000-EP7548	20000803

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000062803	A Based on	WO 200111055
EP 1198575	A1 Based on	WO 200111055

PRIORITY APPLN. INFO: DE 2000-10020996 20000428; DE 1999-19936663  
19990804; DE 1999-19945174 19990921; DE  
1999-19945175 19990921; DE 1999-19948887  
19991011; DE 1999-19953309 19991105

AB WO 200111055 A UPAB: 20010410  
NOVELTY - Functional enzymes which operate in the alternative isoprenoid  
pathway downstream from 2C-methyl-D-erythritol-4-phosphate, are new.  
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are provided for the  
following:  
(1) a protein (P1), in a form that is enzymatically functional for

the conversion of cytidine triphosphate and 2C-methyl-D-erythritol-4-phosphate into 4-diphosphocytidyl-2C-methyl-D-erythritol in the presence of magnesium ions;

(2) a protein (P2), in a form that is enzymatically functional for the conversion of 4-diphosphocytidyl-2C-methyl-D-erythritol in the presence of manganese ions;

(3) a protein (P3), in a form that is enzymatically functional for the conversion of 4-diphosphocytidyl-2C-methyl-D-erythritol and adenosine triphosphate (ATP) into 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate in the presence of a magnesium salt;

(4) a protein (P4), in a form that is enzymatically functional for the conversion of 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate into 2C-methyl-D-erythritol-2,4-cyclopyrophosphate and cytidine monophosphate (CMP);

(5) a protein (P5) in a form that is enzymatically bifunctional, having an N-terminal domain with the function of synthesis of diphosphocytidyl-2C-methyl-D-erythritol from cytidine triphosphate and 2C-methyl-D-erythritol-4-phosphate and a C-terminal domain with the function of the conversion of 4-diphosphocytidyl-2C-methyl-D-erythritol

or

the function of the conversion of 4-diphosphocytidyl-2-C-methyl-D-erythritol-2-phosphate into 2C-methyl-D-erythritol-2,4-cyclopyrophosphate and CMP;

P5 (6) purified isolated nucleic acid (N1) encoding P1, P2, P3, P4 or

and optionally comprising introns;

(7) a **DNA** expression vector comprising N1;

(8) a cell comprising the vector of (7), where the cell is selected from a bacterial, protozoal, fungal, plant, insect or mammalian cell;

(9) a seed comprising a plant cell as defined in (8);

(10) a method (M1) for screening chemical libraries for the presence or absence of **inhibition** of the biosynthesis of isoprenoids by blocking the synthesis of 4-diphosphocytidyl-2C-methyl-D-erythritol from cytidine triphosphate (CTP) and 2C-methyl-D-erythritol-4-phosphate, comprising:

(a) preparing an aqueous mixture comprising P1, 2C-methyl-D-erythritol-4-phosphate or its source, CTP and a divalent metal salt;

(b) reacting the mixture for a predetermined period of time at a predetermined temperature;

(c) detecting the level of conversion to 4-diphosphocytidyl-2C-methyl-D-erythritol;

(d) repeating steps (a) to (c) in the presence of a test sample of a chemical library;

(e) determining the presence or absence of **inhibition** in step (d) by ascertaining whether or not the detected level is lower in

the

presence of the test sample;

(11) a method (M2) for screening chemical libraries for the presence or absence of **inhibition** of the biosynthesis of isoprenoids by blocking the conversion of 4-diphosphocytidyl-2C-methyl-D-erythritol;

(12) a method (M3) for screening chemical libraries for the presence or absence of **inhibition** of the biosynthesis of isoprenoids by blocking the synthesis of 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate from 4-diphosphocytidyl-2C-methyl-D-erythritol and ATP;

(13) a method (M4) for screening chemical libraries for the presence or absence of **inhibition** of the biosynthesis of isoprenoids by blocking the biosynthesis of isoprenoids by blocking the synthesis of 2C-methyl-D-erythritol-2,4-cyclopyrophosphate;



- (14) Isotope labelled 4-diphosphocytidyl-2 C-methyl-D-erythritol, 2C-methyl-D-erythritol-3,4-cyclophosphate, 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate and 2C-methyl-D-erythritol-2,4-cyclopyrophosphate, or their salts;
- (15) a process for forming 4-diphosphocytidyl-2C-methyl-D-erythritol or its salt by reacting CTP and 2C-methyl-D-erythritol-4-phosphate in the presence of P1 and a divalent metal salt;
- (16) a process for forming 2C-methyl-D-erythritol-3,4-cyclophosphate or its salt by reacting 4-diphosphocytidine-2C-methyl-D-erythritol in the presence of P2 and a divalent metal salt;
- (17) a process for forming 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate or its salt by reacting 4-diphosphocytidyl-2C-methyl-D-erythritol with ATP in the presence of P3 and a divalent metal salt;
- (18) a process for forming 2C-methyl-D-erythritol-2,4-cyclopyrophosphate or its salt by reacting 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate with P4;
- (19) a method (M5) for identifying **inhibitor**-resistant variants of P1-P4;
- (20) a variant protein (P6) of P1-P5, where the protein is herbicide resistant;
- (21) a nucleic acid (N2) encoding P6;
- (22) a **DNA** vector comprising N2;
- (23) a cell comprising the vector of (22), where the cell is selected from a bacterial, protozoal, fungal, plant, insect or mammalian cell;
- (24) a seed comprising a plant cell as defined in (23);
- (25) a method for conferring herbicide-resistance in a plant, comprising introducing N2 under conditions in which the nucleic acid is expressed in the plant;
- (26) a method for weed control comprising cultivating a crop containing herbicide-resistant gene having the sequence of N2 in the presence of a weed-controlling effective amount of the herbicide;
- (27) Inhibitor for the biosynthesis of isoprenoids selected from chemical compounds which show enzyme inhibition in accordance with the screening methods of M1-M4;
- (28) a method for the inhibition of the biosynthesis of isoprenoids in plants, bacteria or protozoa by treatment with an inhibitor of (27); and
- (29) a comprehensive process (M6) for preparing intermediates in the isoprenoid pathway downstream from 2C-methyl-D-erythritol 4-phosphate.
- ACTIVITY - None given.  
No biological data given.
- MECHANISM OF ACTION - Isoprenoid biosynthesis inhibitor.  
No biological data given.
- USE - The enzymes are useful for screening a chemical library for inhibitors of the biosynthesis of isoprenoids. 4-diphosphocytidyl-2C-methyl-D-erythritol, 2C-methyl-D-erythritol-2,4-cyclopyrophosphate or 4-diphosphocytidyl-2C-methyl-D-erythritol-2-phosphate, or their salts are useful for screening for inhibitors of the biosynthesis of isoprenoids.
- Herbicide resistant enzymes can be used as genetic markers in any cell that is normally sensitive to the inhibitory effects of herbicide formation. The methods can be used to produce herbicide resistant enzyme variants which can be incorporated into plants to confer selective herbicide resistant on the plants. The methods are also useful for controlling weed by cultivating crops containing herbicide-resistant genes

in the presence of weed-controlling effective amounts of herbicides.  
 The inhibitors are used for inhibiting the biosynthesis of  
 isoprenoids in plants, bacteria or protozoa.  
 Dwg.0/3

L5 ANSWER 10 OF 29 WPIDS (C) 2003 THOMSON DERWENT  
 ACCESSION NUMBER: 2000-350764 [30] WPIDS  
 DOC. NO. CPI: C2000-106790  
 TITLE: Characterizing drug-target interactions and identifying  
 genetic mutations that confer resistance to  
 antibacterial  
 compounds.  
 DERWENT CLASS: B02 B04 C06 D16  
 INVENTOR(S): DUNHAM, S A; OLSON, E  
 PATENT ASSIGNEE(S): (WARN) WARNER LAMBERT CO  
 COUNTRY COUNT: 81  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000024932	A1	20000504	(200030)*	EN	49
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW W: AE AL AU BA BB BG BR CA CN CR CU CZ DM EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT TZ UA US UZ VN YU ZA					
AU 9961607	A	20000515	(200039)		
BR 9914844	A	20010710	(200142)		
EP 1124988	A1	20010822	(200149)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002528094	W	20020903	(200273)		56
MX 2001003289	A1	20011001	(200274)		

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000024932	A1	WO 1999-US22118	19990923
AU 9961607	A	AU 1999-61607	19990923
BR 9914844	A	BR 1999-14844	19990923
		WO 1999-US22118	19990923
EP 1124988	A1	EP 1999-948428	19990923
		WO 1999-US22118	19990923
JP 2002528094	W	WO 1999-US22118	19990923
		JP 2000-578484	19990923
MX 2001003289	A1	MX 2001-3289	20010329

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9961607	A Based on	WO 200024932
BR 9914844	A Based on	WO 200024932
EP 1124988	A1 Based on	WO 200024932
JP 2002528094	W Based on	WO 200024932

PRIORITY APPLN. INFO: US 1998-105965P 19981028  
 AB WO 200024932 A UPAB: 20000624  
 NOVELTY - Methods for identifying and characterizing mutations within

bacterial **DNA** gyrase and FabI that confer resistance to antibacterial compounds, are new. The methods combine random mutagenesis of genes coding for known targets of antibacterial compounds with homologous recombination to identify point mutations resulting in resistance.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a process (I) for identifying and characterizing mutations leading to a selectable phenotype comprising:

- (a) generating a defined set of overlapping 10 kilobase (kb) polymerase chain reaction (PCR) products containing random point mutations which encompass the complete chromosome of an organism;
- (b) transforming pools of 12 PCR product corresponding to 100 kb of the chromosome into a wild-type background;
- (c) isolating strains of bacteria resistant to compound;
- (d) re-transforming sensitive bacteria with individual products (10 kb) from resistant strains to identify a region with 1 or more mutations;
- (e) generating smaller PCR products (1 kb) to further map

mutation(s)

responsible for phenotype; and

(f) sequencing **DNA** from a region conferring resistance to identify the chromosomal mutation;

(2) a process (II) for identifying and characterizing quinolone-**DNA** gyrase interactions using *Neisseria gonorrhoeae* (GC) comprising:

(a) mutagenizing randomly the quinolone resistance determining region

(QRDR) of *gyrA* using oligonucleotide mediated site-specific mutagenesis with a degenerate oligonucleotide or mutagenizing the entire gene using low-fidelity PCR;

(b) transforming these random mutations into a wild-type back-ground;

(c) selecting isogenic quinolone resistant mutations following homologous recombination;

(d) sequencing the *gyrA* QRDR confirming that Ser91 and Asp95 are independently involved in quinolone **inhibition** of **DNA** gyrase;

(e) identifying the following mutation associated with quinolone resistance in *N. gonorrhoeae*: Asp90 to Glu, Ser91 to Cys, Asp95 to His, Glu161 to Gly, Glu161 to Lys, Asn 65 to His, Asp80 to Gly and/or Glu62 to Lys; and

(f) using these mutants to help to understand the mechanism of action of quinolones and other type IV **inhibitors**;

(3) mutations in *N. gonorrhoeae* GyrA associated with quinolone resistance selected from: Asp90 to Glu, Ser91 to Cys, Asp95 to His, Glu161

to Gly, Glu161 to Lys, Asn 65 to His, Asp80 to Gly and/or Glu62 to Lys;

(4) a process (III) for identifying and characterizing a mechanism of

action of an antibacterial compound comprising:

(a) generating **DNA** fragments by PCR amplification of **DNA** from bacteria under conditions that allow for mutations of the fragments;

(b) allowing 1 or more of the generated **DNA** fragments to be incorporated into the chromosome of a bacteria by homologous recombination;

(c) isolating the bacteria that demonstrate resistance to an antibacterial compound; and

- (d) identifying the mutation contained in the **DNA** fragment;
- (5) a process (IV) for identifying mutations contained in the chromosome of a bacteria that results in an identifiable phenotype comprising:
  - (a) generating **DNA** fragments by PCR amplification of the bacterial chromosome corresponding to regions of the bacterial chromosome which may contain a mutation;
  - (b) allowing 1 or more of the **DNA** fragments to be incorporated into the chromosome of a bacteria that does not display the identifiable phenotype by homologous recombination;
  - (c) isolating bacteria that demonstrate the identifiable phenotype;
  - (d) repeating steps (a) to (c) until a single **DNA** fragment less than 10 kb in length is identified as being responsible for the phenotype; and
  - (e) identifying the mutation contained in the **DNA** fragments;
- (6) bacteria (V) comprising a protein in which a contiguous stretch of 40 amino acids is at least 30% identical to residues 75-114 of the *N. gonorrhoeae* GyrA and the residue analogous to:
  - (a) 62 is Lys;
  - (b) 63 is Arg or Glu;
  - (c) 65 is His;
  - (d) 135 is Val; or
  - (e) 161 is Glu, Lys or Arg;
- (7) a protein (VI) comprising a contiguous stretch of 40 amino acids is at least 30% identical to residues 75-114 of the *N. gonorrhoeae* GyrA and the residue analogous to (6a)-(6e) (above);
- (8) bacteria (VII) comprising a protein that is at least 30% identical to the sequence of the *N. gonorrhoeae* FabI protein in which the amino acid residue corresponding to:
  - (a) 15 is Val;
  - (b) 20 is Thr;
  - (c) 23 is Gly;
  - (d) 25 is Val;
  - (e) 51 is Thr;
  - (f) 91 is Thr;
  - (g) 93 is Cys or Ser;
  - (h) 95 is Val;
  - (i) 104 is Leu;
  - (j) 105 is His;
  - (k) 144 is Val;
  - (l) 147 is His;
  - (m) 159 is Ala;
  - (n) 160 is isoLeu;
  - (o) 162 is Val;
  - (p) 193 is Asp or Val;
  - (q) 201 is Val;
  - (r) 203 is Tyr or Val;
  - (s) 204 is Ser, Leu, isoLeu or Val;
  - (t) 212 is Thr or Val; or
  - (u) 247 is Asp;
- (9) a protein (VIII) comprising a sequence at least 30% identical to the sequence of *N. gonorrhoeae* FabI protein comprising the amino acids (8a)-(8u); and
- (10) a process for screening compounds for antibacterial activity comprising:
  - (a) generating DNA fragments by PCR amplification of DNA from the entire genome of a bacteria under conditions that allow for mutation of the fragments;
  - (b) allowing 1 or more of the generated PCR fragments to be

incorporated into the chromosome of a bacteria by homologous recombination;

(c) isolating the bacteria that demonstrate resistance to an antibacterial compound;

(d) identifying the mutation contained in the DNA fragment;

(e) contacting the bacteria with compounds; and

(f) evaluating the compounds for antibacterial activity.

USE - The methods are used for identifying and characterizing drug-target interactions (claimed). The antibacterial strains generated can be used to provide information that could be used or developed for treating bacterial infections of humans, other animals and plants.

ADVANTAGE - The mutations provide valuable information about the molecular target of a compound and how the target and compound interact. The methods allow the simultaneous creation and identification of mutations that confer resistance to antibacterial compounds.

Dwg.0/4

L5 ANSWER 11 OF 29 WPIDS (C) 2003 THOMSON DERWENT  
ACCESSION NUMBER: 2000-148084 [14] WPIDS  
CROSS REFERENCE: 2000-161479 [49]  
DOC. NO. CPI: C2000-046503  
TITLE: Design of antibiotics for inhibition of microorganism  
cell division comprises testing for compounds which  
block

the s-adenosylmethionine-dependent step of crosswall  
formation during cell division.

DERWENT CLASS: B04 D16  
INVENTOR(S): NEWMAN, E B  
PATENT ASSIGNEE(S): (NEWM-I) NEWMAN E B  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
CA 2255460	A1	19990615	(200014)*	EN	28

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CA 2255460	A1	CA 1998-2255460	19981211

PRIORITY APPLN. INFO: CA 1997-2224776 19971215

AB CA 2255460 A UPAB: 20000323

NOVELTY - Designing antibiotics comprises testing compounds which inhibit microorganism cell division by blocking the s-adenosylmethionine (SAM)-dependent step of formation of crosswall during cell division in microorganisms.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method to screen genes and proteins which require modification by SAM comprising:

(a) cloning genes coding for prospective targets on a variable expression vector; and

(b) determining an inducer level which produces filamentation; and

(2) a method to screen compounds for their ability to inhibit the SAM-dependent step comprising:

(a) producing filaments in metK cells carrying a fstZ-green fluorescent protein fusion; and

(b) determining a rate of constriction of the fstZ ring and the conversion of filaments to normal cells in the presence of compounds of interest.

USE - These tests identify a new target for antibiotic design, the yabC gene product which catalyzes the SAM-dependent step. Compounds which induce or repress the yabBC promoter or increase production of the yabC gene product and inhibitors of the yabC SAM-dependent methylase can be used as antibiotics.

Dwg.0/2

L5 ANSWER 12 OF 29 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-126438 [11] WPIDS

CROSS REFERENCE: 2000-105801 [09]; 2000-105811 [09]; 2000-105814 [09];  
2000-105815 [09]; 2000-105826 [09]; 2000-105827 [09];  
2000-105828 [09]; 2000-105829 [09]; 2000-116431 [10];  
2000-116432 [10]; 2000-116448 [10]; 2000-116449 [10];  
2000-116450 [10]; 2000-116451 [10]; 2000-116452 [10];  
2000-116453 [10]; 2000-126427 [11]; 2000-126428 [11];  
2000-126429 [11]; 2000-126430 [11]; 2000-126435 [11];  
2000-126436 [11]; 2000-126437 [11]; 2000-126439 [11];  
2000-126440 [11]; 2000-136825 [12]; 2000-136826 [12];  
2000-136829 [12]; 2000-136830 [12]; 2000-136831 [12];  
2000-147073 [13]; 2000-147074 [13]; 2000-147075 [13];  
2000-160447 [14]; 2000-160448 [14]; 2000-160453 [14];  
2000-160454 [14]; 2000-170778 [15]; 2000-181984 [16];  
2000-181985 [16]; 2000-181986 [16]; 2000-182022 [16];  
2000-328378 [28]; 2002-672820 [72]

DOC. NO. NON-CPI: N2000-095317

DOC. NO. CPI: C2000-038458

TITLE: New multibinding compounds with enhanced biological and/or therapeutic effect (e.g. increased specificity, potency, efficacy and duration of action), useful as antibacterial agents and in animal feed to improve

growth

of livestock.

DERWENT CLASS: B05 S03

INVENTOR(S): FATHEREE, P; GRIFFIN, J H; JUDICE, J K; PACE, J L

PATENT ASSIGNEE(S): (ADME-N) ADVANCED MEDICINE INC

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9964051	A1	19991216	(200011)*	EN	102
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB					
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU					
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR					
TT UA UG US UZ VN YU ZA ZW					
AU 9944266	A	19991230	(200022)		
EP 1083920	A1	20010321	(200117)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9964051	A1	WO 1999-US12779	19990607
AU 9944266	A	AU 1999-44266	19990607

EP 1083920 A1

EP 1999-927332 19990607  
WO 1999-US12779 19990607

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9944266	A Based on	WO 9964051
EP 1083920	A1 Based on	WO 9964051

PRIORITY APPLN. INFO: US 1998-93072P 19980716; US 1998-88448P  
19980608

AB WO 9964051 A UPAB: 20021113

NOVELTY - Multibinding compounds (I) and their salts are new.

DETAILED DESCRIPTION - Multibinding compounds of formula (I) and their salts are new.

L = ligand comprising ligand domain capable of **inhibiting** bacterial Type II **DNA** topoisomerase;

X = linker;

p = 2-10; and

q = 1-20.

INDEPENDENT CLAIMS are also included for:

(1) a method for identifying multimeric ligand compounds that possess

multibinding properties with respect to bacterial Type II **DNA** topoisomerase;

(2) library of multimeric ligand compounds that may possess multibinding properties with respect to bacterial Type II **DNA** topoisomerase.

ACTIVITY - Antibacterial.

Antibacterial activity of test compounds (I) was determined in vitro using **DNA** biosynthesis assay in E. coli H560 cells. Duplicate test samples were blank (boiled cells or cells + TCA or buffer with no cells), control without ATP, control with ATP, test compounds (0.2, 1, 5, 20, 100 and 400 µg/ml) all with ATP. Test compounds (I) were active in this test.

MECHANISM OF ACTION - Bacterial Type II **DNA** topoisomerase **inhibitor**.

USE - Used to treat pathologic conditions alleviated by treatment with antibacterial agents (claimed). Used in animal feed to improve growth of livestock.

ADVANTAGE - Enhanced biological and/or therapeutic effects (e.g. increased specificity, affinity, selectivity, potency, efficacy and therapeutic index, change in duration of action, decreased toxicity and side-effects and improved bioavailability, pharmacokinetics and activity spectrum) compared with prior art compounds. Active against broad spectrum

of **bacteria**, particularly **bacteria** resistant to existing drug therapy, and have high activity and selectivity towards their targets. Bind efficiently to mutant topoisomerases because of reduced energetics of the interaction.

Dwg.0/0

L5 ANSWER 13 OF 29 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1990-051727 [07] WPIDS

CROSS REFERENCE: 1992-066623 [09]

DOC. NO. CPI: C1990-022438

TITLE: Treatment of bacterial infections and identification of bacteria - using anti-sense oligo nucleotide antibiotics

complementary to macromolecular synthesis operon.  
 DERWENT CLASS: B04 D16  
 INVENTOR(S): LUPSKI, J R  
 PATENT ASSIGNEE(S): (BAYU) BAYLOR COLLEGE MEDICINE  
 COUNTRY COUNT: 14  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9000624	A	19900125	(199007)*	EN	36
RW: AT BE CH DE FR GB IT LU NL SE					
W: AU JP					
AU 8937844	A	19900111	(199017)		
AU 8941808	A	19900205	(199032)		
EP 424473	A	19910502	(199118)		
R: AT BE CH DE FR GB IT LU NL SE					
JP 03505672	W	19911212	(199205)		
AU 633495	B	19930204	(199312)		
EP 424473	B1	19960508	(199623)	EN	14
R: AT BE CH DE FR GB IT LI NL SE					
DE 68926455	E	19960613	(199629)		
CA 1340796	C	19991019	(200009)	EN	

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9000624	A	WO 1989-US2884	19890630
EP 424473	A	EP 1989-906671	19890630
JP 03505672	W	JP 1989-509036	19890630
AU 633495	B	AU 1989-37844	19890705
EP 424473	B1	EP 1989-909671	19890630
		WO 1989-US2884	19890630
DE 68926455	E	DE 1989-626455	19890630
		EP 1989-909671	19890630
		WO 1989-US2884	19890630
CA 1340796	C	CA 1989-604846	19890705

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 633495	B Previous Publ.	AU 8937844
EP 424473	B1 Based on	WO 9000624
DE 68926455	E Based on	EP 424473
	Based on	WO 9000624

PRIORITY APPLN. INFO: US 1988-215135 19880705

AB WO 9000624 A UPAB: 20000218

Method of interrupting the expression of a macromolecular synthesis (MMS) operon comprises binding an antisense oligonucleotide to an mRNA transcribed from the MMS operon. Also claimed is a method of identifying bacteria by binding a unique intergenic antisense oligonucleotide to a mRNA transcribed from an MMS operon and determining the amt. of the binding. New antibiotic comprises at least a 10 mer oligonucleotide (I) which is complementary to a sense strand of an MMS operon and binds to a mRNA transcribed by the sense strand. Also claimed are methods of treating bacterial infections by (1) competitively **inhibiting** a recognition site of a protein encoded by an MMS operon by introducing a



competitive oligonucleotide into a bacterium, or (2) interrupting the function of proteins S21, primase or sigma-70. To identify, an MMS operon is treated to form single-stranded **DNA**; an antisense oligonucleotide is bound to a unique intergenic sequence in the single stranded **DNA** of the MMS operon; and the amt. of binding is measured.

USE/ADVANTAGE - By interrupting the expression of the MMS operon, bacterial infections can be treated. By binding of (I) specifically to a unique sequence in the intergenic regions of the MMS operon of **bacteria, bacteria** may be identified. By competitive **inhibition** of the MMS operon gene prods. by using oligonucleotides known to act as recognition sequences for the MMS operon protein prods., bacterial infections may also be treated.

operon  
protein  
prods.,  
bacterial  
infections  
may  
also  
be treated.  
Dwg.0/7  
Dwg.0/7

L5 ANSWER 14 OF 29 WPIDS (C) 2003 THOMSON DERWENT  
ACCESSION NUMBER: 1989-304907 [42] WPIDS  
DOC. NO. CPI: C1989-134995  
TITLE: Recombinant plasmid contg. marked specific gene - used  
to  
construct bacteria used for nitrogen fixing.  
DERWENT CLASS: C03 D16  
PATENT ASSIGNEE(S): (KYOW) KYOWA HAKKO KOGYO KK  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 01225483	A	19890908	(198942)*		14

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 01225483	A	JP 1988-49867	19880304

PRIORITY APPLN. INFO: JP 1988-49867 19880304

AB JP 01225483 A UPAB: 19930923

Recombinant **plasmid** contains nif L gene defected with marker and a nif A gene and promoter integrated upstream of the nif A gene. The recombinant **plasmid** is pNOY9Cm.

Klebsiella sp. bacteria which has N-fixing ability, has a defected nif L gene on the chromosome, a promoter integrated upstream of the nif A gene, and **inhibition** of the N-fixing ability in the presence of ammonia is reduced. The bacteria is Klebsiella oxytoca R16.

Jkevsuekka so, bacteria contains more recombinant **plasmid** integrated by a promoter upstream of the nif A gene. The bacteria is Klebsiella oxytoca R16 (pNOA102).

USE/ADVANTAGE - Bacteria is useful for N-fixing, and the recombinant **plasmid** is used for construction of the **bacteria**. The

**bacteria** expresses N-fixing ability completely.  
0/0

L5 ANSWER 15 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2002:534133 BIOSIS  
DOCUMENT NUMBER: PREV200200534133  
TITLE: Review article: The role of the gut flora in health and disease, and its modification as therapy.  
AUTHOR(S): Hart, A. L.; Stagg, A. J.; Frame, M.; Graffner, H.; Glise, H.; Falk, P.; Kamm, M. A. (1)  
CORPORATE SOURCE: (1) St Mark's Hospital, Watford Road, Harrow, Middlesex, HA1 3UJ: kamm@ic.ac.uk UK  
SOURCE: Alimentary Pharmacology & Therapeutics, (August, 2002) Vol. 16, No. 8, pp. 1383-1393. <http://www.blackwell-science.com/apt.print>.  
ISSN: 0269-2813.  
DOCUMENT TYPE: General Review  
LANGUAGE: English

AB The gut flora is a vast interior ecosystem whose nature is only beginning to be unravelled, due to the emergence of sophisticated molecular tools. Techniques such as 16S ribosomal RNA analysis, polymerase chain reaction amplification and the use of **DNA** microarrays now facilitate rapid identification and characterization of species resistant to conventional culture and possibly unknown species. Life-long cross-talk between the host and the gut flora determines whether health is maintained or disease intervenes. An understanding of these **bacteria-bacteria** and **bacteria**-host immune and epithelial cell interactions is likely to lead to a greater insight into disease pathogenesis. Studies of single organism-epithelial interactions have revealed the large range of metabolic processes that gut bacteria may influence. In inflammatory bowel diseases, bacteria drive the inflammatory process, and genetic predisposition to disease identified to date, such as the recently described NOD2/CARD15 gene variants, may relate to altered bacterial recognition. Extra-intestinal disorders, such as atopy and arthritis, may also have an altered gut milieu as their basis. Clinical evidence is emerging that the modification of this internal environment, using either antibiotics or probiotic bacteria, is beneficial in **preventing** and treating disease. This natural and apparently safe approach holds great appeal.

L5 ANSWER 16 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2000:424364 BIOSIS  
DOCUMENT NUMBER: PREV200000424364  
TITLE: Development of a direct viable count procedure for the investigation of VBNC state in *Listeria monocytogenes*.  
AUTHOR(S): Besnard, V.; Federighi, M.; Cappelier, J. M. (1)  
CORPORATE SOURCE: (1) Unite Mixte de Recherches hygiene des aliments INRA-ENVN, Ecole Nationale Veterinaire de Nantes, Route de Gachet, 44307, Nantes France  
SOURCE: Letters in Applied Microbiology, (July, 2000) Vol. 31, No. 1, pp. 77-81. print.  
ISSN: 0266-8254.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB A viable but non-culturable (VBNC) bacterial state was originally detected

in studies in environmental microbiology. In particular, this state has been demonstrated for a number of human pathogens (*Escherichia coli*, *Salmonella enteritidis*, *Vibrio cholerae*, *Legionella pneumophila* and *Campylobacter jejuni*). The presence of VBNC cells poses a major public health problem since they cannot be detected by traditional culturing methods and the cells remain potentially pathogenic under favourable conditions. But, as far as we know, the VBNC state has not been yet described in *Listeria monocytogenes*. In most studies, this has been assessed by the Kogure procedure based on cellular elongation in the presence of **DNA gyrase inhibitors**. The antibiotic used was nalidixic acid in order to **prevent DNA** replication, only efficient in Gram-negative bacteria studies. In this study, we describe a new DVC procedure to detect and count viable of *L. monocytogenes* suspended in filtered, sterilized distilled water. We used different concentrations of ciprofloxacin, efficient both in

Gram-negative

and Gram-positive **bacteria**. **Bacteria** cells were removed and resuspended in BHI broth, with yeast extract and ciprofloxacin. The mixture was incubated at different incubation times at 37degreeC. After different incubation times, cells were filtered through an isopore polycarbonate black membrane filter and covered with a DAPI solution or orange acridine. The filters were prepared and examined by epifluorescence microscopy. Elongated cells were counted as viable cells, whereas normal size was regarded as nonactive ones. This method allows determination of ciprofloxacin concentration and incubation time optimal to detect maximum viable cells percentage in *L. monocytogenes*.

L5 ANSWER 17 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1994:33778 BIOSIS

DOCUMENT NUMBER: PREV199497046778

TITLE: Characterization of fimbriae produced by enteropathogenic *Escherichia coli*.

AUTHOR(S): Giron, Jorge A. (1); Ho, Alice Suk Yue; Schoolnik, Gary K.

CORPORATE SOURCE: (1) Cent. Vaccine Development, Univ. Maryland, 10 South Pine Street, Baltimore, MD 21201 USA

SOURCE: Journal of Bacteriology, (1993) Vol. 175, No. 22, pp. 7391-7403.  
ISSN: 0021-9193.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Enteropathogenic *Escherichia coli* (EPEC) express rope-like bundles of filaments, termed bundle-forming pili (BFP) (J. A. Giron, A. S. Y. Ho, and

G. K. Schoolnik, Science 254:710-713, 1991). Expression of BFP is associated with localized adherence to HEp-2 cells and the presence of the

EPEC adherence factor **plasmid**. In this study, we describe the identification of rod-like fimbriae and fibrillae expressed simultaneously

on the bacterial surface of three prototype EPEC strains. Upon fimbrial extraction from EPEC B171 (O111:NM), three fimbrial subunits with masses of 16.5, 15.5, and 14.7 kDa were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Their N-terminal amino acid sequence showed homology with F9 and F7-2 fimbriae of uropathogenic *E. coli* and F1845 of diffuse-adhering *E. coli*, respectively. The mixture of fimbrial subunits (called FB171) exhibited mannose-resistant agglutination

of human erythrocytes only, and this activity was not **inhibited** by alpha-D-Gal(1-4)-beta-Gal disaccharide or any other described receptor analogs for P, S, F, M, G, and Dr hemagglutinins of uropathogenic *E. coli*,

which suggests a different receptor specificity. Hemagglutination was **inhibited** by extracellular matrix glycoproteins, i.e., collagen type IV, laminin, and fibronectin, and to a lesser extent by gangliosides, fetuin, and asialofetuin. Scanning electron microscopic studies performed on clusters of bacteria adhering to HEP-2 cells revealed the presence of structures resembling BFP and rod-like fimbriae linking **bacteria** to **bacteria** and **bacteria** to the eukaryotic cell membrane. We suggest a role of these surface appendages in the interaction of EPEC with eukaryotic cells as well as in the overall pathogenesis of intestinal disease caused by EPEC.

L5 ANSWER 18 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1987:207625 BIOSIS

DOCUMENT NUMBER: BA83:105255

TITLE: ANTIBACTERIAL ACTIVITY AND MECHANISM OF ACTION OF 3' AZIDO-3'-DEOXYTHYMIDINE BWA-509U.

AUTHOR(S): ELWELL L P; FERONE R; FREEMAN G A; FYFE J A; HILL J A; RAY P H; RICHARDS C A; SINGER S C; KNICK V B; ET AL

CORPORATE SOURCE: DEP. MICROBIOLOGY, WELLCOME RES. LAB., RESEARCH TRIANGLE PARK, NC 27709.

SOURCE: ANTIMICROB AGENTS CHEMOTHER, (1987) 31 (2), 274-280. CODEN: AMACCQ. ISSN: 0066-4804.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The thymidine analog 3'-azido-3'-deoxythymidine (BWA509U; azidothymidine [AZT]) had potent bactericidal activity against many members of the family

Enterobacteriaceae, including strains of *Escherichia coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Shigella flexneri*, and *Enterobacter aerogenes*. AZT also had bactericidal activity against *Vibrio cholerae* and the fish pathogen *Vibrio anguillarum*. AZT had no activity against *Pseudomonas aeruginosa*, gram-positive **bacteria**, anaerobic **bacteria**, *Mycobacterium tuberculosis*, nontuberculosis mycobacteria, or most fungal pathogens. Several lines of evidence indicated that AZT must be activated to the nucleotide level to **inhibit** cellular metabolism: (i) AZT was a substrate for *Escherichia coli* thymidine kinase; (ii) spontaneously arising AZT-resistant mutants of *E. coli* ML-30 and *S. typhimurium* were deficient in thymidine kinase; and (iii) intact *E. coli* ML-30 cells converted [3H]AZT to its mono-, di-, and triphosphate metabolites. Of the phosphorylated metabolites, AZT-5'-triphosphate was the most potent **inhibitor** of replicative DNA synthesis in toluene-permeabilized *E. coli* pol A mutant cells. AZT-treated *E. coli* cultures grown in minimal medium contained highly elongated cells consistent with the **inhibition** of DNA synthesis. AZT-triphosphate was a specific DNA chain terminator in the in vitro DNA polymerization reaction catalyzed by the Klenow fragment of *E. coli* DNA polymerase I. Thus, DNA chain termination may explain the lethal properties of this compound against susceptible microorganisms.

L5 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1985:306079 BIOSIS

DOCUMENT NUMBER: BA79:86075

TITLE: FURTHER CHARACTERIZATION OF REPAIR OF 8 METHOXYPSORALEN CROSSLINKS IN UV-EXCISION-DEFECTIVE *ESCHERICHIA-COLI*.

AUTHOR(S): BRIDGES B A

CORPORATE SOURCE: MRC CELL MUTATION UNIT, UNIV. SUSSEX, FALMER, BRIGHTON,

SUSSEX BN1 9RR, GREAT BRITAIN.  
SOURCE: MUTAT RES, (1984 (RECD 1985)) 132 (5-6), 153-160.  
CODEN: MUREAV. ISSN: 0027-5107.  
FILE SEGMENT: BA; OLD  
LANGUAGE: English

AB Evidence was previously presented for a new pathway for the repair of 8-methoxypsoralen **DNA** crosslinks. The pathway, which is independent of the uvrA gene but deficient in rep mutants, was now further characterized and shown to be more active in minimal than in nutrient growth media and to be **inhibited** by acriflavine. Although crosslink repair is much reduced in recA bacteria, some still occurs as judged by the effect of acriflavine. By the same criterion, crosslink repair occurs in bacteria with point mutations in the uvrA and uvrB genes, in bacteria with a deletion covering the uvrB gene, and in polA uvrA **bacteria**. **Bacteria** with insertions rather than point mutations in the uvrA gene, although showing evidence of repair, demonstrated minimal **inhibition** with acriflavine suggesting the possibility that the uvrA gene product, even if enzymically inactive, might be able to interact with **DNA** lesions in the presence of acriflavine and **prevent** crosslink repair. Crosslink repair in E. coli WP2 uvrA is associated with base-pair substitution mutagenesis and may be characterized as an error-prone process. Crosslink repair in uvrA bacteria is reduced but not eliminated by a mutation in the umuC gene.

L5 ANSWER 20 OF 29 MEDLINE  
ACCESSION NUMBER: 2002426080 MEDLINE  
DOCUMENT NUMBER: 22170281 PubMed ID: 12182739  
TITLE: The role of the gut flora in health and disease, and its modification as therapy.  
AUTHOR: Hart A L; Stagg A J; Frame M; Graffner H; Glise H; Falk P; Kamm M A  
CORPORATE SOURCE: St. Mark's Hospital, Harrow, Middlesex, UK.  
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2002 Aug) 16 (8)  
1383-93. Ref: 92  
Journal code: 8707234. ISSN: 0269-2813.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200302  
ENTRY DATE: Entered STN: 20020817  
Last Updated on STN: 20030215  
Entered Medline: 20030214

AB The gut flora is a vast interior ecosystem whose nature is only beginning to be unravelled, due to the emergence of sophisticated molecular tools. Techniques such as 16S ribosomal RNA analysis, polymerase chain reaction amplification and the use of **DNA** microarrays now facilitate rapid identification and characterization of species resistant to conventional culture and possibly unknown species. Life-long cross-talk between the host and the gut flora determines whether health is maintained or disease intervenes. An understanding of these **bacteria-bacteria** and **bacteria**-host immune and epithelial cell interactions is likely to lead to a greater insight into disease pathogenesis. Studies of single organism-epithelial interactions have

revealed the large range of metabolic processes that gut bacteria may influence. In inflammatory bowel diseases, bacteria drive the inflammatory process, and genetic predisposition to disease identified to date, such as the recently described NOD2/CARD15 gene variants, may relate to altered bacterial recognition. Extra-intestinal disorders, such as atopy and arthritis, may also have an altered gut milieu as their basis. Clinical evidence is emerging that the modification of this internal environment, using either antibiotics or probiotic bacteria, is beneficial in **preventing** and treating disease. This natural and apparently safe approach holds great appeal.

L5 ANSWER 21 OF 29 MEDLINE  
ACCESSION NUMBER: 2000417319 MEDLINE  
DOCUMENT NUMBER: 20344504 PubMed ID: 10886620  
TITLE: Development of a direct viable count procedure for the investigation of VBNC state in *Listeria monocytogenes*.  
AUTHOR: Besnard V; Federighi M; Cappelier J M  
CORPORATE SOURCE: Unite Mixte de Recherches hygiene des aliments INRA-ENVN, Ecole Nationale Veterinaire de Nantes, Route de Gachet, NANTES, France.  
SOURCE: LETTERS IN APPLIED MICROBIOLOGY, (2000 Jul) 31 (1) 77-81.  
  
Journal code: 8510094. ISSN: 0266-8254.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200009  
ENTRY DATE: Entered STN: 20000915  
Last Updated on STN: 20000915  
Entered Medline: 20000901

AB A viable but non-culturable (VBNC) bacterial state was originally detected in studies in environmental microbiology. In particular, this state has been demonstrated for a number of human pathogens (*Escherichia coli*, *Salmonella enteritidis*, *Vibrio cholerae*, *Legionella pneumophila* and *Campylobacter jejuni*). The presence of VBNC cells poses a major public health problem since they cannot be detected by traditional culturing methods and the cells remain potentially pathogenic under favourable conditions. But, as far as we know, the VBNC state has not been yet described in *Listeria monocytogenes*. In most studies, this has been assessed by the Kogure procedure based on cellular elongation in the presence of **DNA gyrase inhibitors**. The antibiotic used was nalidixic acid in order to **prevent DNA** replication, only efficient in Gram-negative bacteria studies. In this study, we describe a new DVC procedure to detect and count viable of *L. monocytogenes* suspended in filtered, sterilized distilled water. We used different concentrations of ciprofloxacin, efficient both in Gram-negative and Gram-positive **bacteria**. **Bacteria** cells were removed and resuspended in BHI broth, with yeast extract and ciprofloxacin. The mixture was incubated at different incubation times at 37 degrees C. After different incubation times, cells were filtered through an isopore polycarbonate black membrane filter and covered with a DAPI solution or orange acridine. The filters were prepared and examined by epifluorescence microscopy. Elongated cells were counted as viable cells, whereas normal size was regarded as nonactive ones. This method allows determination of ciprofloxacin concentration and incubation time

optimal to detect maximum viable cells percentage in *L. monocytogenes*.

L5 ANSWER 22 OF 29 MEDLINE

ACCESSION NUMBER: 94042915 MEDLINE  
DOCUMENT NUMBER: 94042915 PubMed ID: 7901197  
TITLE: Characterization of fimbriae produced by enteropathogenic *Escherichia coli*.  
AUTHOR: Giron J A; Ho A S; Schoolnik G K  
CORPORATE SOURCE: Department of Microbiology and Immunology, Howard Hughes Medical Institute, Stanford University, California 94305.  
CONTRACT NUMBER: DK 38707 (NIDDK)  
SOURCE: JOURNAL OF BACTERIOLOGY, (1993 Nov) 175 (22) 7391-403.  
Journal code: 2985120R. ISSN: 0021-9193.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199312  
ENTRY DATE: Entered STN: 19940117  
Last Updated on STN: 19970203  
Entered Medline: 19931214

AB Enteropathogenic *Escherichia coli* (EPEC) express rope-like bundles of filaments, termed bundle-forming pili (BFP) (J. A. Giron, A. S. Y. Ho, and G. K. Schoolnik, *Science* 254:710-713, 1991). Expression of BFP is associated with localized adherence to HEp-2 cells and the presence of the EPEC adherence factor **plasmid**. In this study, we describe the identification of rod-like fimbriae and fibrillae expressed simultaneously on the bacterial surface of three prototype EPEC strains. Upon fimbrial extraction from EPEC B171 (O111:NM), three fimbrial subunits with masses of 16.5, 15.5, and 14.7 kDa were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Their N-terminal amino acid sequence showed homology with F9 and F7(2) fimbriae of uropathogenic *E. coli* and F1845 of diffuse-adhering *E. coli*, respectively. The mixture of fimbrial subunits (called FB171) exhibited mannose-resistant agglutination of human erythrocytes only, and this activity was not **inhibited** by alpha-D-Gal(1-4)-beta-Gal disaccharide or any other described receptor analogs for P, S, F, M, G, and Dr hemagglutinins of uropathogenic *E. coli*, which suggests a different receptor specificity. Hemagglutination was **inhibited** by extracellular matrix glycoproteins, i.e., collagen type IV, laminin, and fibronectin, and to a lesser extent by gangliosides, fetuin, and asialofetuin. Scanning electron microscopic studies performed on clusters of bacteria adhering to HEp-2 cells revealed the presence of structures resembling BFP and rod-like fimbriae linking **bacteria** to **bacteria** and **bacteria** to the eukaryotic cell membrane. We suggest a role of these surface appendages in the interaction of EPEC with eukaryotic cells as well as in the overall pathogenesis of intestinal disease caused by EPEC.

L5 ANSWER 23 OF 29 MEDLINE

ACCESSION NUMBER: 87183451 MEDLINE  
DOCUMENT NUMBER: 87183451 PubMed ID: 3551832  
TITLE: Antibacterial activity and mechanism of action of 3'-azido-3'-deoxythymidine (BW A509U).

AUTHOR: Elwell L P; Ferone R; Freeman G A; Fyfe J A; Hill J A; Ray P H; Richards C A; Singer S C; Knick V B; Rideout J L; +  
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1987 Feb) 31 (2) 274-80.  
Journal code: 0315061. ISSN: 0066-4804.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 198705  
ENTRY DATE: Entered STN: 19900303  
Last Updated on STN: 19970203  
Entered Medline: 19870520

AB The thymidine analog 3'-azido-3'-deoxythymidine (BW A509U; azidothymidine [AZT]) had potent bactericidal activity against many members of the family

Enterobacteriaceae, including strains of Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Shigella flexneri, and Enterobacter aerogenes. AZT also had bactericidal activity against Vibrio cholerae and the fish pathogen Vibrio anguillarum. AZT had no activity against Pseudomonas aeruginosa, gram-positive **bacteria**, anaerobic **bacteria**, Mycobacterium tuberculosis, nontuberculosis mycobacteria, or most fungal pathogens. Several lines of evidence indicated that AZT must be activated to the nucleotide level to **inhibit** cellular metabolism: AZT was a substrate for E. coli thymidine kinase; spontaneously arising AZT-resistant mutants of E. coli ML-30 and S. typhimurium were deficient in thymidine kinase; and intact

E.

coli ML-30 cells converted [3H]AZT to its mono-, di-, and triphosphate metabolites. Of the phosphorylated metabolites, AZT-5'-triphosphate was the most potent **inhibitor** of replicative **DNA** synthesis in toluene-permeabilized E. coli pol A mutant cells. AZT-treated E. coli cultures grown in minimal medium contained highly elongated cells consistent with the **inhibition** of **DNA** synthesis. AZT-triphosphate was a specific **DNA** chain terminator in the in vitro **DNA** polymerization reaction catalyzed by the Klenow fragment of E. coli **DNA** polymerase I. Thus, **DNA** chain termination may explain the lethal properties of this compound against susceptible microorganisms.

L5 ANSWER 24 OF 29 MEDLINE

ACCESSION NUMBER: 85086074 MEDLINE  
DOCUMENT NUMBER: 85086074 PubMed ID: 6096705  
TITLE: Further characterization of repair of 8-methoxypsoralen crosslinks in UV-excision-defective Escherichia coli.  
AUTHOR: Bridges B A  
SOURCE: MUTATION RESEARCH, (1984 Nov-Dec) 132 (5-6) 153-60.  
Journal code: 0400763. ISSN: 0027-5107.  
PUB. COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198502  
ENTRY DATE: Entered STN: 19900320  
Last Updated on STN: 19900320  
Entered Medline: 19850208

AB Evidence was previously presented for a new pathway for the repair of 8-methoxypsoralen **DNA** crosslinks. The pathway, which is independent of the uvrA gene but deficient in rep mutants, has now been further characterized and shown to be more active in minimal than in



nutrient growth media and to be **inhibited** by acriflavine. Although crosslink repair is much reduced in recA bacteria, some still occurs as judged by the effect of acriflavine. By the same criterion, crosslink repair occurs in bacteria with point mutations in the uvrA and uvrB genes, in bacteria with a deletion covering the uvrB gene, and in polA uvrA **bacteria**. **Bacteria** with insertions rather than point mutations in the uvrA gene, although showing evidence of repair, demonstrated minimal **inhibition** with acriflavine suggesting the possibility that the uvrA gene product, even if enzymically inactive, might be able to interact with **DNA** lesions in the presence of acriflavine and **prevent** crosslink repair. Crosslink repair in E. coli WP2 uvrA is associated with base-pair substitution mutagenesis and may be characterized as an error-prone process. Crosslink repair in uvrA bacteria is reduced but not eliminated by a mutation in the umuC gene.

L5 ANSWER 25 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002309976 EMBASE

TITLE: Review article: The role of the gut flora in health and disease, and its modification as therapy.

AUTHOR: Hart A.L.; Stagg A.J.; Frame M.; Graffner H.; Glise H.; Falk P.; Kamm M.A.

CORPORATE SOURCE: Prof. M.A. Kamm, St Mark's Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, United Kingdom. kamm@ic.ac.uk

SOURCE: Alimentary Pharmacology and Therapeutics, (2002) 16/8 (1383-1393).

Refs: 92

ISSN: 0269-2813 CODEN: APTHEN

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology  
030 Pharmacology  
037 Drug Literature Index  
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The gut flora is a vast interior ecosystem whose nature is only beginning to be unravelled, due to the emergence of sophisticated molecular tools. Techniques such as 16S ribosomal RNA analysis, polymerase chain reaction amplification and the use of **DNA** microarrays now facilitate rapid identification and characterization of species resistant to conventional culture and possibly unknown species. Life-long cross-talk between the host and the gut flora determines whether health is maintained

or disease intervenes. An understanding of these **bacteria-bacteria** and **bacteria**-host immune and epithelial cell interactions is likely to lead to a greater insight into disease pathogenesis. Studies of single organism-epithelial interactions have revealed the large range of metabolic processes that gut bacteria may influence. In inflammatory bowel diseases, bacteria drive the inflammatory process, and genetic predisposition to disease identified to date, such as

the recently described NOD2/CARD15 gene variants, may relate to altered bacterial recognition. Extra-intestinal disorders, such as atopy and arthritis, may also have an altered gut milieu as their basis. Clinical evidence is emerging that the modification of this internal environment, using either antibiotics or probiotic bacteria, is beneficial in

preventing and treating disease. This natural and apparently safe approach holds great appeal.

L5 ANSWER 26 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000251922 EMBASE

TITLE: Development of a direct viable count procedure for the investigation of VBNC state in *Listeria monocytogenes*.

AUTHOR: Besnard V.; Federighi M.; Cappelier J.M.

CORPORATE SOURCE: J.M. Cappelier, Unite Mixte Recher. hygiene aliments, INRA-ENVN, Ecole Natl. Veterinaire de Nantes, Route de Gachet, 44307 Nantes, France. cappelier@vet-nantes.fr

SOURCE: Letters in Applied Microbiology, (2000) 31/1 (77-81).

Refs: 22

ISSN: 0266-8254 CODEN: LAMIE7

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB V. BESNARD, M. FEDERIGHI AND J.M. CAPPELIER. 2000 A viable but non-culturable (VBNC) bacterial state was originally detected in studies in environmental microbiology. In particular, this state has been demonstrated for a number of human pathogens (*Escherichia coli*, *Salmonella*

*enteritidis*, *Vibrio cholerae*, *Legionella pneumophila* and *Campylobacter jejuni*). The presence of VBNC cells poses a major public health problem since they cannot be detected by traditional culturing methods and the cells remain potentially pathogenic under favourable conditions. But, as far as we know, the VBNC state has not been yet described in *Listeria monocytogenes*. In most studies, this has been assessed by the Kogure procedure based on cellular elongation in the presence of **DNA gyrase inhibitors**. The antibiotic used was nalidixic acid in order to **prevent DNA** replication, only efficient in Gram-negative bacteria studies. In this study, we describe a new DVC procedure to detect and count viable of *L. monocytogenes* suspended in filtered, sterilized distilled water. We used different concentrations of ciprofloxacin, efficient both in Gram-negative and Gram-positive **bacteria**. **Bacteria** cells were removed and resuspended in BHI broth, with yeast extract and ciprofloxacin. The mixture was

incubated

at different incubation times at 37.degree.C. After different incubation times, cells were filtered through an isopore polycarbonate black

membrane

filter and covered with a DAPI solution or orange acridine. The filters were prepared and examined by epifluorescence microscopy. Elongated cells were counted as viable cells, whereas normal size was regarded as nonactive ones. This method allows determination of ciprofloxacin concentration and incubation time optimal to detect maximum viable cells percentage in *L. monocytogenes*.

L5 ANSWER 27 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 93339334 EMBASE

DOCUMENT NUMBER: 1993339334

TITLE: Characterization of fimbriae produced by enteropathogenic *Escherichia coli*.

AUTHOR: Giron J.A.; Ho A.S.Y.; Schoolnik G.K.

CORPORATE SOURCE: Center for Vaccine Development, University of Maryland, 10 South Pine St., Baltimore, MD 21201, United States

SOURCE: Journal of Bacteriology, (1993) 175/22 (7391-7403).

ISSN: 0021-9193 CODEN: JOBAAY

COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 004 Microbiology  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Enteropathogenic Escherichia coli (EPEC) express rope-like bundles of filaments, termed bundle-forming pili (BFP) (J. A. Giron, A. S. Y. Ho, and G. K. Schoolnik, Science 254:710-713, 1991). Expression of BFP is associated with localized adherence to HEP-2 cells and the presence of the EPEC adherence factor **plasmid**. In this study, we describe the identification of rod-like fimbriae and fibrillae expressed simultaneously on the bacterial surface of three prototype EPEC strains. Upon fimbrial extraction from EPEC B171 (O111:NM), three fimbrial subunits with masses of 16.5, 15.5, and 14.7 kDa were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Their N-terminal amino acid sequence showed homology with F9 and F72 fimbriae of uropathogenic E. coli and F1845 of diffuse-adhering E. coli, respectively. The mixture of fimbrial subunits (called FB171) exhibited mannose-resistant agglutination of human erythrocytes only, and this activity was not **inhibited** by .alpha.-D-Gal(1-4)-.beta.-Gal disaccharide or any other described receptor analogs for P, S, F, M, G, and Dr hemagglutinins of uropathogenic E. coli, which suggests a different receptor specificity.

Hemagglutination was **inhibited** by extracellular matrix glycoproteins, i.e., collagen type IV, laminin, and fibronectin, and to a lesser extent by gangliosides, fetuin, and asialofetuin. Scanning electron microscopic studies performed on clusters of bacteria adhering to HEP-2 cells revealed the presence of structures resembling BFP and rod-like fimbriae linking **bacteria to bacteria** and **bacteria** to the eukaryotic cell membrane. We suggest a role of these surface appendages in the interaction of EPEC with eukaryotic cells as well as in the overall pathogenesis of intestinal disease caused by EPEC.

L5 ANSWER 28 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 87078751 EMBASE

DOCUMENT NUMBER: 1987078751

TITLE: Antibacterial activity and mechanism of action of 3'-azido-3'-deoxythymidine (BW A509U).

AUTHOR: Elwell L.P.; Ferone R.; Freeman G.A.; et al.

CORPORATE SOURCE: Department of Microbiology, Wellcome Research Laboratories,

SOURCE: Research Triangle Park, NC 27709, United States  
Antimicrobial Agents and Chemotherapy, (1987) 31/2 (274-280).

CODEN: AMACCQ

COUNTRY: United States

DOCUMENT TYPE: Journal

FILE SEGMENT: 037 Drug Literature Index

004 Microbiology

006 Internal Medicine

LANGUAGE: English

AB The thymidine analog 3'-azido-3'-deoxythymidine (BW A509U; azidothymidine

[AZT]) had potent bactericidal activity against many members of the family

Enterobacteriaceae, including strains of *Escherichia coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Shigella flexneri*, and *Enterobacter aerogenes*. AZT also had bactericidal activity against *Vibrio cholerae* and the fish pathogen *Vibrio anguillarum*. AZT had no activity against *Pseudomonas aeruginosa*, gram-positive **bacteria**, anaerobic **bacteria**, *Mycobacterium tuberculosis*, nontuberculosis mycobacteria, or most fungal pathogens. Several lines of evidence indicated that AZT must be activated to the nucleotide level to **inhibit** cellular metabolism: (i) AZT was a substrate for *E. coli* thymidine kinase; (ii) spontaneously arising AZT-resistant mutants of *E. coli* ML-30 and *S. typhimurium* were deficient in thymidine kinase; and (iii) intact *E. coli* ML-30 cells converted [3H]AZT to its mono-, di-, and triphosphate metabolites. Of the phosphorylated metabolites, AZT-5'-triphosphate was the most potent **inhibitor** of replicative **DNA** synthesis in toluene-permeabilized *E. coli* pol A mutant cells. AZT-treated *E. coli* cultures grown in minimal medium contained highly elongated cells consistent with the **inhibition** of **DNA** synthesis. AZT-triphosphate was a specific **DNA** chain terminator in the in vitro **DNA** polymerization reaction catalyzed by the Klenow fragment of *E. coli* **DNA** polymerase I. Thus, **DNA** chain termination may explain the lethal properties of this compound against susceptible microorganisms.

L5 ANSWER 29 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 85027309 EMBASE  
DOCUMENT NUMBER: 1985027309  
TITLE: Further characterization of repair of 8-methoxypsoralen crosslinks in UV-excision-defective *Escherichia coli*.  
AUTHOR: Bridges B.A.  
CORPORATE SOURCE: MRC Cell Mutation Unit, University of Sussex, Falmer, Brighton, Sussex BN1 9RR, United Kingdom  
SOURCE: Mutation Research, (1984) 132/5-6 (153-160).  
CODEN: MUREAV  
COUNTRY: Netherlands  
DOCUMENT TYPE: Journal  
FILE SEGMENT: 037 Drug Literature Index  
022 Human Genetics  
013 Dermatology and Venereology  
052 Toxicology  
014 Radiology  
030 Pharmacology  
004 Microbiology  
LANGUAGE: English

AB Evidence was previously presented for a new pathway for the repair of 8-methoxypsoralen **DNA** crosslinks. The pathway, which is independent of the *uvrA* gene but deficient in *rep* mutants, has now been further characterized and shown to be more active in minimal than in nutrient growth media and to be **inhibited** by acriflavine. Although crosslink repair is much reduced in *recA* bacteria, some still occurs as judged by the effect of acriflavine. By the same criterion, crosslink repair occurs in bacteria with point mutations in the *uvr* and *uvrB* genes, in bacteria with a deletion covering the *uvrB* gene, and in *polA uvrA bacteria*. **Bacteria** with insertions rather than point mutations in the *uvrA* gene, although showing evidence of repair, demonstrated minimal **inhibition** with acriflavine suggesting the possibility that the *uvrA* gene product, even if enzymically inactive, might be able to interact with **DNA** lesions in the

presence of acriflavine and **prevent** crosslink repair. Crosslink repair in E. coli WP2 uvrA is associated with base-pair substitution mutagenesis and may be characterized as an error-prone process. Crosslink repair in uvrA bacteria is reduced but not eliminated by a mutation in the umuC gene.

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(FILE 'HOME' ENTERED AT 17:22:04 ON 19 FEB 2003)

FILE 'CAPLUS, WPIDS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 17:22:41 ON 19 FEB 2003

L1	85846	"BACTERIA-TO-BACTERIA"
L2	384	L1 AND PLASMID AND GENES AND DNA
L3	7	L1 AND TAUROLIDINE
L4	202	L1(P) (PLASMID OR DNA)
L5	29	L4(P) (PREVENT? OR INHIBIT?)

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=> file caplus wpids biosis medline embase

FILE 'CAPLUS' ENTERED AT 16:55:36 ON 19 FEB 2003  
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FILE 'MEDLINE' ENTERED AT 16:55:36 ON 19 FEB 2003

FILE 'EMBASE' ENTERED AT 16:55:36 ON 19 FEB 2003  
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=> s plasmid(p)prevent?(p)bacteria(p)transfer?  
L1 136 PLASMID(P) PREVENT?(P) BACTERIA(P) TRANSFER?

=> l1 and taurolidine  
L2 0 L1 AND TAUROLIDINE

=> s "bacteria-to-bacteria transfer"  
L3 0 "BACTERIA-TO-BACTERIA TRANSFER"

=> s "bacteria-to-bacteria"(p)transfer?(p)DNA  
L4 9 "BACTERIA-TO-BACTERIA"(P) TRANSFER?(P) DNA

=> l1 and l4  
L5 0 L1 AND L4

=> d l4 1-9 ibib ab

L4 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:90224 CAPLUS

DOCUMENT NUMBER: 136:129913

TITLE: Mutational analysis in isolation of regulated  
virulence determinants of bacterial pathogens and the  
rtxA and enhC genes from Legionella pneumophila

INVENTOR(S): Cirillo, Jeffrey D.

PATENT ASSIGNEE(S): The Board of Regents of the University of Nebraska,  
USA

SOURCE: PCT Int. Appl., 131 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008418	A2	20020131	WO 2001-US23306	20010724
WO 2002008418	A3	20020613		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,  
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,

VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2000-628871 A 20000724

AB The present invention relates to novel methods for isolation and identification of virulence determinants from bacterial pathogens. The present invention also relates to novel genes of the Legionella pneumophila bacteria, and methods of detection of Legionella pneumophila bacteria in samples. The present invention relates to novel methods for isolation and identification of virulence determinants from bacterial pathogens. A pool of bacterial mutants with enhanced virulence phenotype is obtained, and the **DNA** responsible as a factor for the enhanced virulence is located. Random mutations are inserted into the **DNA**, the **DNA transferred** into wild-type **bacteria**, and **bacteria** that no longer express the enhanced virulence are selected in order to identify an active site of

the

**DNA** necessary to confer enhanced virulence. The present invention also more specifically relates to novel rtxA and enhC genes of the Legionella pneumophila bacteria. Gene rtxA affects bacterial adherence

to

monocytes and epithelial cells, is involved in cytotoxicity and pore formation by L. pneumophila, and affects the bacterial virulence. These genes allow for the detection and quantitation of L. pneumophila and thus diagnosis of Legionnaires' disease, as well as for the design of inhibitors of the protein products of the genes.

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:110568 CAPLUS

DOCUMENT NUMBER: 135:206077

TITLE: Evidence for extensive resistance gene transfer among Bacteroides spp. and among Bacteroides and other genera in the human colon

AUTHOR(S): Shoemaker, N. B.; Vlamakis, H.; Hayes, K.; Salyers, A.

CORPORATE SOURCE: A.  
Department of Microbiology, University of Illinois, Urbana, IL, 61801, USA

SOURCE: Applied and Environmental Microbiology (2001), 67(2), 561-568

CODEN: AEMIDF; ISSN: 0099-2240

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Transfer** of antibiotic resistance genes by conjugation is thought to play an important role in the spread of resistance. Yet virtually no information is available about the extent to which such horizontal **transfers** occur in natural settings. In this paper, we show that conjugal gene **transfer** has made a major contribution to increased antibiotic resistance in Bacteroides species, a numerically predominant group of human colonic bacteria. Over the past 3 decades, carriage of the tetracycline resistance gene, tetQ, has increased

from about 30% to more than 80% of strains. Alleles of tetQ in different Bacteroides species, with one exception, were 96 to 100% identical at the **DNA** sequence level, as expected if horizontal gene **transfer** was responsible for their spread. Southern blot analyses showed further that **transfer** of tetQ was mediated by a conjugative transposon (CTn) of the CTnDOT type. Carriage of two

erythromycin resistance genes, ermF and ermG, rose from <2 to 23% and accounted for about 70% of the total erythromycin resistances obsd. Carriage of tetQ and the erm genes was the same in isolates taken from healthy people with no recent history of antibiotic use as in isolates obtained from patients with Bacteroides infections. This finding indicates that resistance **transfer** is occurring in the community and not just in clin. environments. The high percentage of strains that are carrying these resistance genes in people who are not taking antibiotics is consistent with the hypothesis that once acquired, these resistance genes are stably maintained in the absence of antibiotic selection. Six recently isolated strains carried ermB genes. Two were identical to erm(B)-P from Clostridium perfringens, and the other four had

only one to three mismatches. The nine strains with ermG genes had **DNA** sequences that were more than 99% identical to the ermG of Bacillus sphaericus. Evidently, there is a genetic conduit open between gram-pos. **bacteria**, including **bacteria** that only pass through the human colon, and the gram-neg. Bacteroides species. Our results support the hypothesis that extensive gene **transfer** occurs among bacteria in the human colon, both within the genus Bacteroides and among Bacteroides species and gram-pos. bacteria.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:93810 CAPLUS

DOCUMENT NUMBER: 135:106091

TITLE: Bacteria-mediated DNA transfer for gene therapy and genetic vaccination

AUTHOR(S): Weiss, Siegfried; Chakraborty, Trinad

CORPORATE SOURCE: Molecular Immunology, GBF-National Research Center Biotechnol., Braunschweig, D-38124, Germany

SOURCE: Development of Novel Antimicrobial Agents: Emerging Strategies (2001), 81-89. Editor(s): Lohner, Karl. Horizon Scientific Press: Wymondham, UK.  
CODEN: 69AXXR

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review, with 25 refs. Transfer of eukaryotic expression plasmids to mammalian cells has recently been achieved using live attenuated bacteria.

These successes have encouraged the use and generation of bacterial vector

delivery systems that use local, mucosal and systemic routes of infection to deliver the desired gene directly to the cell type or organ of interest. Intrinsic properties of invasive bacteria such as their

tropism

for cell types or cell to cell spread are currently understood in great detail and provide the necessary basis for the design of novel vehicles. Finally, the ability of bacteria to harbor very large plasmids makes them very attractive as vehicles for gene therapy. Escherichia coli rendered artificially invasive and Listeria monocytogenes were used in vitro to transfer reporter genes into various types of cells from different species. Transfer could also be obsd. in vivo with L. monocytogenes albeit at low frequency. Shigella flexneri, Salmonella typhimurium and Salmonella typhi were used as vehicles to transfer plasmids for genetic immunization in vivo. Immune responses against the antigen encoded by

the



expression plasmid could be detected in all cases. Thus, bacteria represent a simple and versatile carrier system for genetic immunization that should provide the flexibility required for the various vaccination problems. The low prodn. cost of such vaccines makes them attractive candidates for mass application.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12666 CAPLUS

DOCUMENT NUMBER: 134:96206

TITLE: General method for isolation of regulated virulence determinants from bacterial pathogens and the rtxA and

enhC genes from Legionella pneumophila

INVENTOR(S): Cirillo, Jeffrey D.

PATENT ASSIGNEE(S): The Board of Regents of the University of Nebraska, USA

SOURCE: PCT Int. Appl., 105 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000877	A2	20010104	WO 2000-US17743	20000627
WO 2001000877	A3	20020510		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002086304	A1	20020704	US 2001-881901	20010615
US 2002086981	A1	20020704	US 2001-882583	20010615
PRIORITY APPLN. INFO.:			US 1999-141717P	P 19990630
			US 2000-604561	A3 20000627

AB The present invention relates to novel methods for isolation and identification of virulence determinants from bacterial pathogens. A pool

of bacterial mutants with enhanced virulence phenotype is obtained, and the DNA responsible as a factor for the enhanced virulence is located. Random mutations are inserted into the DNA, the DNA transferred into wild-type bacteria, and bacteria that no longer express the enhanced virulence are selected in order to identify an active site of the DNA necessary to confer enhanced virulence. The present invention also more specifically relates to novel rtxA and enhC genes of the Legionella pneumophila bacteria. Gene rtxA affects bacterial adherence to monocytes and epithelial cells, is involved in cytotoxicity and pore formation by

L. pneumophila, and affects the bacterial virulence. These genes allow for the detection and quantitation of L. pneumophila and thus diagnosis of

Legionnaires' disease, as well as for the design of inhibitors of the protein products of the genes.

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1973:156890 CAPLUS  
DOCUMENT NUMBER: 78:156890  
TITLE: Transcription of spontaneously released bacterial deoxyribonucleic acid in frog auricles  
AUTHOR(S): Stroun, Maurice; Anker, Philippe  
CORPORATE SOURCE: Dep. Plant Physiol., Univ. Geneva, Geneva, Switz.  
SOURCE: Journal of Bacteriology (1973), 114(1), 114-20  
CODEN: JOBAAY; ISSN: 0021-9193  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB After frog auricles have been in contact with a suspension of **bacteria** of **bacteria**-free supernatant fluid, newly synthesized bacterial RNA is recovered in animal cells. Evidently the presence of bacterial **DNA**-dependent RNA polymerase is necessary for the transcription of bacterial **DNA** in the host cells. This seems to be related to a **transfer** of **DNA** and **DNA**-dependent RNA polymerase from bacteria into animal cells.

L4 ANSWER 6 OF 9 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1997-065167 [06] WPIDS  
CROSS REFERENCE: 1995-240663 [31]  
DOC. NO. CPI: C1997-021401  
TITLE: Prod'n. of heterologous non-bacterial protein in bacteria - using a chromosomal transfer DNA contg. a gene which has not been cloned in a multi-copy vector.  
DERWENT CLASS: B04 D16  
INVENTOR(S): MASCARENHAS, D; OLSON, P S; OLSON, P  
PATENT ASSIGNEE(S): (CELT-N) CELTRIX PHARM INC  
COUNTRY COUNT: 72  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9640722	A1	19961219	(199706)*	EN	80
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN					
AU 9659864	A	19961230	(199716)		
NO 9705748	A	19980119	(199813)		
CZ 9703944	A3	19980617	(199830)		
EP 859782	A1	19980826	(199838)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT SE SI					
AU 697444	B	19981008	(199901)		
NZ 309645	A	19981223	(199906)		
US 5861273	A	19990119	(199911)		
HU 9900868	A2	19990628	(199931)		
JP 11507521	W	19990706	(199937)		76
KR 99022717	A	19990325	(200024)		
CN 1190403	A	19980812	(200273)		
JP 3358818	B2	20021224	(200304)		42

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
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WO 9640722	A1		WO 1996-US9006	19960605
AU 9659864	A		AU 1996-59864	19960605
NO 9705748	A		WO 1996-US9006	19960605
			NO 1997-5748	19971205
CZ 9703944	A3		WO 1996-US9006	19960605
			CZ 1997-3944	19960605
EP 859782	A1		EP 1996-917207	19960605
			WO 1996-US9006	19960605
AU 697444	B		AU 1996-59864	19960605
NZ 309645	A		NZ 1996-309645	19960605
			WO 1996-US9006	19960605
US 5861273	A	CIP of	US 1993-170588	19931221
			US 1995-482182	19950607
HU 9900868	A2		WO 1996-US9006	19960605
			HU 1999-868	19960605
JP 11507521	W		WO 1996-US9006	19960605
			JP 1997-501431	19960605
KR 99022717	A		WO 1996-US9006	19960605
			KR 1997-709159	19971208
CN 1190403	A		CN 1996-195423	19960605
JP 3358818	B2		WO 1996-US9006	19960605
			JP 1997-501431	19960605

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9659864	A	Based on	WO 9640722
CZ 9703944	A3	Based on	WO 9640722
EP 859782	A1	Based on	WO 9640722
AU 697444	B	Previous Publ.	AU 9659864
		Based on	WO 9640722
NZ 309645	A	Based on	WO 9640722
US 5861273	A	CIP of	US 5470727
HU 9900868	A2	Based on	WO 9640722
JP 11507521	W	Based on	WO 9640722
KR 99022717	A	Based on	WO 9640722
JP 3358818	B2	Previous Publ.	JP 11507521
		Based on	WO 9640722

PRIORITY APPLN. INFO: US 1995-482182 19950607; US 1993-170588  
19931221

AB WO 9640722 A UPAB: 20030117

A method of producing a heterologous protein (A) comprises: (a) transferring a chromosomal DNA (I) into a bacterial host cell pref. comprising a chromosome, where (I) contains at least one copy of a gene encoding (A) and a selectable marker; (b) selecting for integration of (I) into the cell resulting in a host cell chromosome comprising a gene encoding (A) operably linked to a promoter functional in the host cell and a selectable marker flanked by duplicate DNA: and (c) expressing the gene, where the gene is at no time operably linked to a promoter, functional in the host cell, on a multicopy number plasmid vector during construction of the transfer DNA and where (A) accumulates within the host cell to a level in excess of 0.1% of total cell protein.

USE - The method is used to produce heterologous, pref. a non-bacterial, protein in a bacterial host cell such as E. coli to a level in excess of 1% of total cell protein. It is esp. useful for producing an eukaryotic esp. a mammalian protein.

ADVANTAGE - The method of construction avoids the generation of low or high multicopy plasmid where expression of a small amt. of the foreign protein may be toxic to the cell. The method allows high accumulation of the foreign protein (about 20% of total cell protein) from low (approx.

2) copies of the gene encoding (A).  
Dwg.0/26

L4 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:151564 BIOSIS

DOCUMENT NUMBER: PREV200100151564

TITLE: Evidence for extensive resistance gene transfer among Bacteroides spp. and among Bacteroides and other genera in the human colon.

AUTHOR(S): Shoemaker, N. B.; Vlamakis, H.; Hayes, K.; Salyers, A. A. (1)

CORPORATE SOURCE: (1) Department of Microbiology, UIUC, 601 South Goodwin Ave., B103 CLSL, Urbana, IL, 61801: abigails@life.uiuc.edu USA

SOURCE: Applied and Environmental Microbiology, (February, 2001) Vol. 67, No. 2, pp. 561-568. print.  
ISSN: 0099-2240.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB **Transfer** of antibiotic resistance genes by conjugation is thought to play an important role in the spread of resistance. Yet virtually no information is available about the extent to which such horizontal **transfers** occur in natural settings. In this paper, we show that conjugal gene **transfer** has made a major contribution to increased antibiotic resistance in Bacteroides species, a numerically predominant group of human colonic bacteria. Over the past 3 decades, carriage of the tetracycline resistance gene, tetQ, has increased

from about 30% to more than 80% of strains. Alleles of tetQ in different Bacteroides species, with one exception, were 96 to 100% identical at the DNA sequence level, as expected if horizontal gene **transfer** was responsible for their spread. Southern blot analyses showed further that **transfer** of tetQ was mediated by a conjugative transposon (CTn) of the CTnDOT type. Carriage of two erythromycin resistance genes, ermF and ermG, rose from <2 to 23% and accounted for about 70% of the total erythromycin resistances observed. Carriage of tetQ and the erm genes was the same in isolates taken from healthy people with no recent history of antibiotic use as in isolates obtained from patients with Bacteroides infections. This finding indicates

that resistance **transfer** is occurring in the community and not just in clinical environments. The high percentage of strains that are carrying these resistance genes in people who are not taking antibiotics is consistent with the hypothesis that once acquired, these resistance genes are stably maintained in the absence of antibiotic selection. Six recently isolated strains carried ermB genes. Two were identical to erm(B)-P from Clostridium perfringens, and the other four had only one to three mismatches. The nine strains with ermG genes had DNA sequences that were more than 99% identical to the ermG of Bacillus

sphaericus. Evidently, there is a genetic conduit open between gram-positive **bacteria**, including **bacteria** that only pass through the human colon, and the gram-negative Bacteroides species. Our results support the hypothesis that extensive gene **transfer** occurs among bacteria in the human colon, both within the genus Bacteroides and among Bacteroides species and gram-positive bacteria.

L4 ANSWER 8 OF 9 MEDLINE  
ACCESSION NUMBER: 2001381324 MEDLINE  
DOCUMENT NUMBER: 21091943 PubMed ID: 11157217  
TITLE: Evidence for extensive resistance gene transfer among Bacteroides spp. and among Bacteroides and other genera in the human colon.  
AUTHOR: Shoemaker N B; Vlamakis H; Hayes K; Salyers A A  
CORPORATE SOURCE: Department of Microbiology, University of Illinois, Urbana, Illinois 61801, USA.  
CONTRACT NUMBER: AI22383 (NIAID)  
SOURCE: APPLIED AND ENVIRONMENTAL MICROBIOLOGY, (2001 Feb) 67 (2) 561-8.  
Journal code: 7605801. ISSN: 0099-2240.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200107  
ENTRY DATE: Entered STN: 20010709  
Last Updated on STN: 20010709  
Entered Medline: 20010705

AB **Transfer** of antibiotic resistance genes by conjugation is thought to play an important role in the spread of resistance. Yet virtually no information is available about the extent to which such horizontal **transfers** occur in natural settings. In this paper, we show that conjugal gene **transfer** has made a major contribution to increased antibiotic resistance in Bacteroides species, a numerically predominant group of human colonic bacteria. Over the past 3 decades, carriage of the tetracycline resistance gene, tetQ, has increased

from about 30% to more than 80% of strains. Alleles of tetQ in different Bacteroides species, with one exception, were 96 to 100% identical at the DNA sequence level, as expected if horizontal gene **transfer** was responsible for their spread. Southern blot analyses showed further that **transfer** of tetQ was mediated by a conjugative transposon (CTn) of the CTnDOT type. Carriage of two erythromycin resistance genes, ermF and ermG, rose from <2 to 23% and accounted for about 70% of the total erythromycin resistances observed. Carriage of tetQ and the erm genes was the same in isolates taken from healthy people with no recent history of antibiotic use as in isolates obtained from patients with Bacteroides infections. This finding indicates

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gram-positive **bacteria**, including **bacteria** that only pass through the human colon, and the gram-negative *Bacteroides* species. Our results support the hypothesis that extensive gene **transfer** occurs among bacteria in the human colon, both within the genus *Bacteroides* and among *Bacteroides* species and gram-positive bacteria.

L4 ANSWER 9 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
ACCESSION NUMBER: 2001053313 EMBASE  
TITLE: Evidence for extensive resistance gene transfer among *Bacteroides* spp. and among *Bacteroides* and other genera in the human colon.  
AUTHOR: Shoemaker N.B.; Vlamakis H.; Hayes K.; Salyers A.A.  
CORPORATE SOURCE: A.A. Salyers, Department of Microbiology - UIUC, B103 CLSL,  
601 South Goodwin Ave., Urbana, IL 61801, United States.  
abigails@life.uiuc.edu  
SOURCE: Applied and Environmental Microbiology, (2001) 67/2 (561-568).  
Refs: 52  
ISSN: 0099-2240 CODEN: AEMIDF  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 004 Microbiology  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB **Transfer** of antibiotic resistance genes by conjugation is thought to play an important role in the spread of resistance. Yet virtually no information is available about the extent to which such horizontal **transfers** occur in natural settings. In this paper, we show that conjugal gene **transfer** has made a major contribution to increased antibiotic resistance in *Bacteroides* species, a numerically predominant group of human colonic bacteria. Over the past 3 decades, carriage of the tetracycline resistance gene, *tetQ*, has increased from about 30% to more than 80% of strains. Alleles of *tetQ* in different *Bacteroides* species, with one exception, were 96 to 100% identical at the DNA sequence level, as expected if horizontal gene **transfer** was responsible for their spread. Southern blot analyses showed further that **transfer** of *tetQ* was mediated by a conjugative transposon (CTn) of the CTnDOT type. Carriage of two erythromycin resistance genes, *ermF* and *ermG*, rose from <2 to 23% and accounted for about 70% of the total erythromycin resistances observed. Carriage of *tetQ* and the *erm* genes was the same in isolates taken from healthy people with no recent history of antibiotic use as in isolates obtained from patients with *Bacteroides* infections. This finding indicates that resistance **transfer** is occurring in the community and not just in clinical environments. The high percentage of strains that are carrying these resistance genes in people who are not taking antibiotics is consistent with the hypothesis that once acquired, these resistance genes are stably maintained in the absence of antibiotic selection. Six recently isolated strains carried *ermB* genes. Two were identical to *erm(B)-P* from *Clostridium perfringens*, and the other four had only one to three mismatches. The nine strains with *ermG* genes had DNA sequences that were more than 99% identical to the *ermG* of *Bacillus sphaericus*. Evidently, there is a genetic conduit open between gram-positive **bacteria**, including **bacteria** that only pass through the human colon, and the gram-negative *Bacteroides* species. Our results support the hypothesis that extensive gene **transfer** occurs among bacteria in the human colon, both within the genus

Bacteroides and among Bacteroides species and gram-positive bacteria.

=> l4 and taurolidine

L6           0 L4 AND TAUROLIDINE

=> d his

(FILE 'HOME' ENTERED AT 16:55:01 ON 19 FEB 2003)

FILE 'CAPLUS, WPIDS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 16:55:36 ON 19  
FEB 2003

L1           136 S PLASMID(P) PREVENT?(P) BACTERIA(P) TRANSFER?

L2           0 L1 AND TAUROLIDINE

L3           0 S "BACTERIA-TO-BACTERIA TRANSFER"

L4           9 S "BACTERIA-TO-BACTERIA"(P) TRANSFER?(P) DNA

L5           0 L1 AND L4

L6           0 L4 AND TAUROLIDINE

=> logoff y

show files

File 155:MEDLINE(R) 1966-2002/Aug W3

File 5:Biosis Previews(R) 1969-2002/Aug W2  
(c) 2002 BIOSIS

File 315:ChemEng & Biotec Abs 1970-2002/Jul  
(c) 2002 DECHEMA

File 73:EMBASE 1974-2002/Aug W3  
(c) 2002 Elsevier Science B.V.

?ds

Set	Items	Description
S1	94	AU=COSTIN J? OR AU=COSTIN, J?
S2	374	TAUROLIDINE
S3	174	TAUROLIN?
S4	886	THIADIAZINE?
S5	1323	METHYLENEBIS?
S6	1075708	RESISTAN?
S7	228365	STAPH?
S8	38984	VANCOMYCIN
S9	827907	TRANSFER?
S10	441220	PLASMID? OR VECTOR? ?
S11	2667214	BACTERI?
S12	399891	ADHES? OR ADHER?
S13	2	S1 AND (S2 OR S3 OR (S4(5N)S5))
S14	423	(S2 OR S3 OR (S4(5N)S5))
S15	20	S14 AND (S6(5N) (ANTIBIOTIC? ? OR VANCOMYCIN))
S16	15	S14 AND S7 AND S6
S17	2	S14 AND S10
S18	27	S15-S17
S19	29	S13 OR S15-S17
S20	21	RD S19 (unique items)

?t 20/7/all

20/7/1 (Item 1 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

13308217 22001262 PMID: 12006145

A randomized double-blinded placebo-controlled crossover trial of nebulized taurolidine in adult cystic fibrosis patients infected with *Burkholderia cepacia*.

Ledson Martin J; Gallagher Malcolm J; Robinson Maxine; Cowperthwaite Carolyn; Williets Trevor; Hart Charles A; Walshaw Martin J

Regional Adult Cystic Fibrosis Unit, Liverpool University, Liverpool, United Kingdom.

Journal of aerosol medicine : the official journal of the International Society for Aerosols in Medicine (United States) Spring 2002, 15 (1) p51-7, ISSN 0894-2684 Journal Code: 8809251

Document type: Clinical Trial; Journal Article; Randomized Controlled Trial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

*Burkholderia cepacia* is an aggressive pathogen that colonizes cystic fibrosis (CF) patients, causing greatly increased morbidity and mortality. It is resistant to most antibiotics, but sensitive in vitro to a novel agent, taurolidine. This has not previously been used against *B. cepacia*, nor given in nebulized form. We assessed the effect of nebulized



taurolidine on United Kingdom epidemic (ET12) *B. cepacia* infection in 20 adult CF patients attending our regional adult cystic fibrosis outpatient clinic using a prospective, randomized, double-blinded placebo-controlled crossover trial. Nebulized taurolidine (4 mL 2% solution) or saline (4 mL 0.9% solution) was given twice daily. Each arm lasted 4 weeks, with a 2-week intervening washout period. Sputum *B. cepacia* colony counts (primary outcome measure), spirometry, and symptoms (secondary outcome measures) were assessed. Eighteen patients completed the study. There was no change in *B. cepacia* colony counts or spirometry, nor symptom scores. We conclude that, although taurolidine is well tolerated in nebulized form, in this study it had no in vivo anti-*B. cepacia* activity.

Record Date Created: 20020513

20/7/2 (Item 2 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

10732600 20277911 PMID: 10817739

Activities of taurolidine in vitro and in experimental enterococcal endocarditis.

Torres-Viera C; Thauvin-Eliopoulos C; Souli M; DeGirolami P; Farris M G; Wennersten C B; Sofia R D; Eliopoulos G M

Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02115, USA.

Antimicrobial agents and chemotherapy (UNITED STATES) Jun 2000, 44 (6) p1720-4, ISSN 0066-4804 Journal Code: 0315061

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In vitro, the antimicrobial agent taurolidine inhibited virtually all of the bacteria tested, including vancomycin - resistant enterococci, oxacillin-resistant staphylococci, and *Stenotrophomonas maltophilia*, at concentrations between 250 and 2,000 microg/mL. Taurolidine was not effective in experimental endocarditis. While it appears unlikely that this antimicrobial would be useful for systemic therapy, its bactericidal activity and the resistance rates found (<10<sup>-9</sup>) are favorable indicators for its possible development for topical use.

Record Date Created: 20000711

20/7/3 (Item 3 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

09516741 97411522 PMID: 9333700

1996 pathogen incidence and resistance status in peritonitis]  
Erregerhaufigkeit und Resistenzsituation bei Peritonitis 1996.

Focht J; Nosner K

Institut für Laboruntersuchungen, Moers.

Langenbecks Archiv für Chirurgie (GERMANY) 1997, 382 (4 Suppl 1) pS1-4, ISSN 0023-8236 Journal Code: 0204167

Document type: Journal Article ; English Abstract

Languages: GERMAN

Main Citation Owner: NLM

Record type: Completed

Severe intra-abdominal infection is associated with a high mortality rate. In addition to risk factors in the patients, the causal pathogens and

the selection of appropriate therapeutic procedures play an essential part in the course of these conditions. In the majority of intra-abdominal infections mixed aerobic/anaerobic infections, mostly with some involvement of enterobacteria and also of enterococci and staphylococci can be demonstrated. In addition to surgical intervention a calculated antimicrobial initial treatment of intra-abdominal infections with an antibiotic with an adequate effect to combat the pathogen concerned can contribute to improving the patient's prognosis. A calculated antibiotic treatment can only be effectively and reliably carried through if the frequency of the pathogen and the resistance situation are known. Retrospective evaluations of data on the sensitivity and frequency of pathogens from a defined group of subjects allow conclusions on the epidemiological situation in a particular catchment area or in a medical sector and thus make it possible to calculate the appropriate therapy for infections. In 1996 a total of 2,779 bacterial isolates from the intra-abdominal infection sector were examined: 935 Enterobacteriaceae, 83 nonfermenters, 177 Staphylococcus spp., 211 Enterococcus spp., 39 Streptococcus spp., and 1334 different anaerobic bacteria. Fresh clinical isolates were available for all pathogens tested. The most frequent gram-negative pathogen was *E. coli* (60%) and the most frequent gram-positive pathogen, *E. faecalis* (44%); the most frequent anaerobic pathogen was *B. fragilis* (39%). Taurolidine had the lowest resistance rate against gram-negative and anaerobic pathogens. Teicoplanin had the highest activity against gram-positive pathogens.

Record Date Created: 19971015

20/7/4 (Item 4 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

07848858 93380383 PMID: 8370323

Taurolidine : in vitro activity against multiple- antibiotic - resistant , nosocomially significant clinical isolates of *Staphylococcus aureus*, *Enterococcus faecium*, and diverse Enterobacteriaceae.

Traub W H; Leonhard B; Bauer D

Institut für Medizinische Mikrobiologie und Hygiene, Universität des Saarlandes, Homburg/Saar, BRD.

Chemotherapy (SWITZERLAND) Sep-Oct 1993, 39 (5) p322-30, ISSN 0009-3157 Journal Code: 0144731

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Taurolidine at  $< \text{ or } = 1,250$  micrograms/ml killed all 37 isolates of multiple- antibiotic - resistant *Staphylococcus aureus* ( $n = 9$ ), *Enterococcus faecium* ( $n = 17$ ), and Enterobacteriaceae ( $n = 11$ ). Time-kill experiments disclosed that bovine serum (65% v/v) only marginally retarded the bactericidal activity of 2,000 and 1,000 micrograms/ml of taurolidine against the various strains. Taurolidine at 2,000 micrograms/ml did not antagonize the bactericidal activity of 50% (v/v) fresh human serum against promptly and delayed serum-sensitive test strains of *Escherichia coli* and *Serratia marcescens*. In the presence of 65% (v/v) of fresh defibrinated human blood from two donors, however, the bactericidal activity of this antimicrobial compound was delayed, i.e., manifested only following extended (overnight) incubation, against staphylococcal and enterococcal isolates, though less so in the case of Enterobacteriaceae. Taurolidine at 2,000 micrograms/ml killed ingested, i.e., intraphagocytic bacteria of

human-serum- resistant *S. marcescens* strains CDC 06:H3 and P016:H-.

Record Date Created: 19931008

20/7/5 (Item 5 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

07788337 93314363 PMID: 8325127

*Enterococcus faecium*: in vitro activity of antimicrobial drugs, singly and combined, with and without defibrinated human blood, against multiple-antibiotic - resistant strains.

Traub W H; Leonhard B; Bauer D

Institut für Medizinische Mikrobiologie und Hygiene, Universität des Saarlandes, Homburg/Saar, BRD.

Chemotherapy (SWITZERLAND) Jul-Aug 1993, 39 (4) p254-64, ISSN 0009-3157 Journal Code: 0144731

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The minimal inhibitory (MICs) and bactericidal concentrations of 14 antimicrobial drugs were determined against 17 clinical isolates of *Enterococcus faecium*, including 4 glycopeptide-resistant strains. Both teicoplanin and vancomycin lacked bactericidal activity against all 13 susceptible isolates. Time-kill experiments served to test various antibiotic combinations chiefly against glycopeptide-resistant strains in Mueller-Hinton broth (MHB) and in MHB supplemented with 65% (v/v) fresh defibrinated human blood. Co-trimoxazole, fusidic acid, and novobiocin yielded bacteriostatic effects. Rifampin was bactericidally active against rifampin-susceptible strains (MICs = 0.125 micrograms/ml), but less so against low-level-rifampin-resistant (MICs = 2-8 micrograms/ml) strains in MHB. However, in the presence of human blood, rifampin (2 micrograms/ml) combined with co-trimoxazole (0.25/4.75 micrograms/ml) killed rifampin-susceptible and low-level-rifampin-resistant, but not moderate-level-rifampin-resistant (MICs = 16-32 micrograms/ml) strains of *E. faecium*. Of two topical drugs examined, mupirocin merely inhibited strains of *E. faecium*; conversely, taurolidine at 2,000 micrograms/ml was efficacious against all strains examined, although the kinetics of bactericidal activity were retarded somewhat in the presence of 65 vol% human blood.

Record Date Created: 19930810

20/7/6 (Item 6 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

06623499 90324089 PMID: 2197257

[Value of systemic and local administration of antibiotics in soft tissue and bone infections]

Stellenwert systemischer und lokaler Antibiotika-Anwendung bei Weichteil- und Knocheninfekten.

Rittmann W W; Schawalder K; Enzler M

Klinik für Chirurgie, Kantonsspital St. Gallen.

Helvetica chirurgica acta (SWITZERLAND) Apr 1990, 56 (6) p879-89, ISSN 0018-0181 Journal Code: 2985095R

Document type: Journal Article; Review; Review, Tutorial ; English Abstract

Languages: GERMAN

Main Citation Owner: NLM

Record type: Completed

There is little data to support the efficacy of prophylactic antibiotics in traumatology. In closed fractures three randomized controlled studies using a 1-3 day prophylaxis with Cephalosporins of the first or second generation or a Penicillinase-resistant Penicillin demonstrated a reduction of the infection rate. For the Cephalosporins of the second generation it was shown, that a single dose was less efficient than five repeated applications over 24 hours. In hip-fractures a prophylaxis with Cephalothin or Cefotiam reduced the frequency of infections when compared with controls. In open fractures a treatment over 10 days using Cephalothin or Isoxazolyl-Penicillin showed a significant drop of the infection rate. If however the fractures were not treated using the principles of rigid internal fixation and were covered with Dicloxacillin over 2 days only there was no significant improvement. A multicenter study finally indicates that a one day course of cefonicid sodium is not inferior to a prolonged course of antibiotics for prevention of early postoperative fracture-site infections. We conclude, that open and closed fractures can profit from antibiotic prophylaxis which starts immediately before surgery and is continued over 24 hours. We favour Isoxazolyl-Penicillin because of its efficacy against staphylococcus aureus and epidermidis which predominate in early infection. In established bone and soft tissue infections antibiotics are used when there is local spreading, sepsis, involvement of joints or when reinterventions in the infectious focus are necessary. In these cases bacteriological testing in the laboratory is essential for the selection of antibiotics. Local application of antibiotics in irrigation-drainage solutions can not be recommended. PMMA-chains serve as temporary spacers, but should be removed early before their extraction becomes difficult and resistant bacteria develop. When defects are closed with cancellous bone or soft tissues the use of Gentamycin-fleece or Taurolin -gels is recommended. (9 Refs.)

Record Date Created: 19900824

20/7/7 (Item 7 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

03502043 81036513 PMID: 6107015

Nebacetin and taurolin as intraoperative disinfectant solutions in surgery of the locomotor system (author's transl)]

Nebacetin und Taurolin als intraoperative Spullosungen bei Eingriffen am Bewegungsapparat.

Burri C; Lob G; Rudzki M

Aktuelle Traumatologie (GERMANY, WEST) Apr 1980, 10 (2) p65-72,  
ISSN 0044-6173 Journal Code: 0421405

Document type: Journal Article ; English Abstract

Languages: GERMAN

Main Citation Owner: NLM

Record type: Completed

The anti-infective preventive action of intraoperative disinfection with physiological solution containing antibiotics, appears to be firmly established, judging from numerous publications. Since germs are showing a world-wide increasing resistance, the search for antibiotics which continue to be effective must be kept up, but alternative suggestions are equally necessary. Some publications have already been presented indicating that success similar to that previously obtained with antibiotics is

possible by using disinfectants in the prophylaxis and treatment of infections. Hence, a comparative study was conducted using the non-absorbable broad-spectrum antibiotic Nebacetin and the disinfectant Taurolin in a 1% solution with a group of patients subjected to a total of 7699 major and minor surgical operations. Prospectively, early infections during the stay of the patient in the hospital, as well as disturbed wound healing, were included. No significant difference was found in the number of infections and the rate of disturbed wound healing. Indirectly, it is possible to conclude with the help of results from literature that the disinfectant Taurolin is suitable as an addition to intra-operative rinsing in the prophylaxis of infections.

Record Date Created: 19801216

20/7/8 (Item 1 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13671063 BIOSIS NO.: 200200299884  
Stability and efficacy of antibiotic-anticoagulant lock solutions for central venous catheter-related sepsis.  
AUTHOR: Droste Jan C(a); Farrington Ken(a); Macdonald Alan; Jeraj Hassan A  
AUTHOR ADDRESS: (a)Renal Medicine, Lister Hospital, Stevenage\*\*UK  
JOURNAL: Journal of the American Society of Nephrology 12 (Program and Abstract Issue):p376A September, 2001  
MEDIUM: print  
CONFERENCE/MEETING: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001  
ISSN: 1046-6673  
RECORD TYPE: Citation  
LANGUAGE: English

20/7/9 (Item 2 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13649297 BIOSIS NO.: 200200278118  
Compositions and methods for treating infections of the ear.  
AUTHOR: Costin James C (a  
AUTHOR ADDRESS: (a)Lower Gwynedd, PA\*\*USA  
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1255 (4):pNo Pagination Feb. 26, 2002  
MEDIUM: e-file  
ISSN: 0098-1133  
DOCUMENT TYPE: Patent  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The use of 4,4- methylenebis (tetrahydro-1,2,4- thiadiazine -1,2-dioxide) in treating infections of the ear.

20/7/10 (Item 3 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13575513 BIOSIS NO.: 200200204334

Prevention of hemodialysis catheter-related bloodstream infection using an antimicrobial lock.

AUTHOR: Quarello Francesco(a); Forneris Giacomo

AUTHOR ADDRESS: (a)Divisione di Nefrologia e Dialisi, Ospedale San Giovanni Bosco, Piazza Donatore di Sangue, 3, I-10154, Torino\*\*Italy E-Mail: fquarello@tin.it

JOURNAL: Blood Purification 20 (1):p87-92 2002

MEDIUM: print

ISSN: 0253-5068

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Among currently available vascular access options for hemodialysis, central venous catheters show the poorest reliability, with frequent complications of thrombosis and stenosis impairing patency. The most serious problem, however, is catheter-related bloodstream infection (CRBI), which is typically a cause for removal of the catheter and protracted systemic antibiotic therapy. In our experience, a totally implanted device (Dialock(R), Bioline Corp.) seems to confer a better global protection against catheter-related infections than standard tunneled catheters, accounting for 0.97 vs. 4.75 infection episodes/1,000 catheter-days, respectively ( $p < 0.001$ ). Bloodstream infection rates, however, are not statistically different in the two groups (0.85 vs. 0.81 per 1,000 catheter-days;  $p = n.s.$ ), indicating that the improvement is mainly related to local cutaneous infections. On the other hand, in the Sodemann experience, a new taurolidine-based lock solution (Neutrolin(R), Bioline Corp.) greatly reduced CRBI rates with both subcutaneous ports and tunneled catheters to 0.29 and 0.20 episodes/1,000 catheter-days, respectively. These promising results await further confirmation from ongoing clinical trials.

20/7/11 (Item 4 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13209918 BIOSIS NO.: 200100417067

Compositions and methods for the management of Crohn's disease.

AUTHOR: Costin James C (a

AUTHOR ADDRESS: (a)Belle Mead, NJ\*\*USA

JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1247 (4):pNo Pagination June 26, 2001

MEDIUM: e-file

ISSN: 0098-1133

DOCUMENT TYPE: Patent

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The present invention relates to a method of treating a human infected with Crohn's disease comprising enterally administering to the individual in need of such treatment an effective amount of a composition comprising 4,4'-methylenebis-(tetrahydro-1,2,4-thiadiazine)-1,1,1',1'-tetraoxide, commonly known as taurolidine.

20/7/12 (Item 5 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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11577809 BIOSIS NO.: 199800358505

Taurolidine 2 percent as an antimicrobial lock solution for prevention of recurrent catheter-related bloodstream infections.

AUTHOR: Jurewitsch Brian(a); Lee Tundra; Park Joan; Jeejeebhoy Khursheed

AUTHOR ADDRESS: (a)Dep. Pharmacy, St. Michael's Hosp., Toronto, ON M5B 1W8

\*\*Canada

JOURNAL: Journal of Parenteral and Enteral Nutrition 22 (4):p242-244

July-Aug., 1998

ISSN: 0148-6071

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: This case report describes our preliminary data on the use of taurolidine as a lock technique. Taurolidine is a novel antimicrobial agent that has found a niche in Europe for prevention of bacteremia in home parenteral nutrition (HPN) patients who have multiple catheter-related bloodstream infections. Methods: A 29-year-old male with short bowel syndrome was admitted 18 times in 9 years for treatment of Gram-positive, Gram-negative, and yeast-associated catheter-related bloodstream infections. Management consisted of conventional antibiotic treatment in accordance with blood culture and sensitivity results as well as catheter removal in 10 cases. Ten months before the last infection, the patient was instructed to instil 1.5 mL taurolidine 2% daily into his central line after finishing his HPN infusion and has continued to do so 2 years to date. Results: The incidence of catheter-related bloodstream infections decreased from 8.5 to 1.5 infections per 1000 catheter days. Conclusions: These data support previous observations made outside North America and suggest that taurolidine may prove to be an effective and safe antimicrobial agent for the prevention of recurrent catheter-related bloodstream infections.

20/7/13 (Item 6 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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11087302 BIOSIS NO.: 199799708447

Spectrum of pathogens and resistance in peritonitis.

AUTHOR: Focht J(a); Noesner K

AUTHOR ADDRESS: (a)Biosci., Inst. Laboruntersuchungen, Zum  
Schuermannsgraben 30, D-47441 Moers\*\*Germany

JOURNAL: Langenbecks Archiv fuer Chirurgie 382 (4 SUPPL. 1):pS1-S4 1997

ISSN: 0023-8236

RECORD TYPE: Abstract

LANGUAGE: German; Non-English

SUMMARY LANGUAGE: German; English

ABSTRACT: Severe intra-abdominal infection is associated with a high mortality rate. In addition to risk factors in the patients, the causal pathogens and the selection of appropriate therapeutic procedures play an essential part in the course of these conditions. In the majority of

intra-abdominal infections mixed aerobic/anaerobic infections, mostly with some involvement of enterobacteria and also of enterococci and staphylococci can be demonstrated. In addition to surgical intervention a calculated antimicrobial initial treatment of intra-abdominal infections with an antibiotic with an adequate effect to combat the pathogen concerned can contribute to improving the patient's prognosis. A calculated antibiotic treatment can only be effectively and reliably carried through if the frequency of the pathogen and the resistance situation are known. Retrospective evaluations of data on the sensitivity and frequency of pathogens from a defined group of subjects allow conclusions on the epidemiological situation in a particular catchment area or in a medical sector and thus make it possible to calculate the appropriate therapy for infections. In 1996 a total of 2,779 bacterial isolates from the intra-abdominal infection sector were examined: 935 Enterobacteriaceae, 83 nonfermenters, 177 Staphylococcus spp., 211 Enterococcus spp., 39 Streptococcus spp., and 1334 different anaerobic bacteria. Fresh clinical isolates were available for all pathogens tested. The most frequent gram-negative pathogen was E. coli (60%) and the most frequent gram-positive pathogen, E. faecalis (44%); the most frequent anaerobic pathogen was B. fragilis (39%). Taurolocline had the lowest resistance rate against gram-negative and anaerobic pathogens. Teicoplanin had the highest activity against gram-positive pathogens.

20/7/14 (Item 7 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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02152387 BIOSIS NO.: 000063067390  
TAUROLIN A NEW CHEMO THERAPEUTIC AGENT  
AUTHOR: BROWNE M K; LESLIE G B; PFIRRMANN R W  
JOURNAL: J APPL BACTERIOL 41 (3). 1976 (RECD 1977) 363-368. 1976  
FULL JOURNAL NAME: Journal of Applied Bacteriology  
CODEN: JABAA  
RECORD TYPE: Abstract

ABSTRACT: Taurolin, bis-(1,1-dioxo-perhydro-1,2,4-thiadiazinyl-4)-methan, is a novel, broad spectrum, nonsystemic chemotherapeutic agent. It is effective in vivo against a wide range of pathogenic organisms including Pseudomonas aeruginosa, Escherichia coli, Proteus vulgaris and Salmonella typhimurium, and would be of particular use against antibiotic-resistant organisms. It is based on an endogenous substance, taurine, which acts as a non-toxic formaldehyde carrier donating methylol groups to bacterial protein and endotoxin thus causing denaturation and polycondensation of the pathogens and their pyrogens. Taurolin may be of value in the treatment of fecal peritonitis.

20/7/15 (Item 1 from file: 73)  
DIALOG(R)File 73:EMBASE  
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11615278 EMBASE No: 2002182965  
Antimicrobial activity of a novel catheter lock solution  
Shah C.B.; Mittelman M.W.; Costerton J.W.; Parenteau S.; Pelak M.;  
Arsenault R.; Mermel L.A.  
L.A. Mermel, Division of Infectious Diseases, Rhode Island Hospital, 593



Eddy St., Providence, RI 02903 United States  
AUTHOR EMAIL: lmermel@lifespan.org  
Antimicrobial Agents and Chemotherapy ( ANTIMICROB. AGENTS CHEMOTHER. ) ( United States) 2002, 46/6 (1674-1679)  
CODEN: AMACC ISSN: 0066-4804  
DOCUMENT TYPE: Journal ; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 28

Intravascular catheter-associated bloodstream infections significantly increase rates of morbidity and hospital costs. Microbial colonization and development of biofilms, which are known to be recalcitrant to antibiotic therapy, often lead to the loss of otherwise patent vascular access systems. We evaluated a new taurolidine - and citrate-based catheter lock solution (Neutrolin; Biolink Corporation, Norwell, Mass.) for its activity against planktonic microbes, antimicrobial activity in a catheter model, and biofilm eradication activity. In studies of planktonic microbes, after 24 h of contact, 675 mg of taurolidine -citrate solution per liter caused >99% reductions in the initial counts of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. A solution of 13,500 mg/liter was cidal for *Candida albicans*. Ports and attached catheters inoculated with 50 to 600 CFU of these bloodstream isolates per ml were locked with heparin or the taurolidine -citrate solution. After 72 h, there was no growth in the taurolidine -citrate-treated devices but the heparin-treated devices exhibited growth in the range of  $6 \times 10^2$  to  $5 \times 10^6$  CFU/ml. Biofilms were developed on silicone disks in modified Robbins devices with broth containing 6% serum (initial counts,  $10^6$  to  $10^8$  CFU/cm<sup>2</sup>). The axenic biofilms were treated for 24 h with taurolidine -citrate or heparin. Taurolidine -citrate exposure resulted in a median reduction of 4.8 logs, whereas heparin treatment resulted in a median reduction of 1.7 logs ( $P < 0.01$ ). No significant differences in the effects of the two treatments against *P. aeruginosa* and *C. albicans* were observed. These findings suggest that taurolidine -citrate is a promising combination agent for the prevention and treatment of intravascular catheter-related infections.

20/7/16 (Item 2 from file: 73)  
DIALOG(R)File 73:EMBASE  
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11193813 EMBASE No: 2001203139  
Therapy of infection  
Rommes J.H.; Rios G.; Zandstra D.F.  
J.H. Rommes, Department of Intensive Care, Gelre Ziekenhuizen, PO Box 9014, 7300 DS Apeldoorn Netherlands  
Current Anaesthesia and Critical Care ( CURR. ANAESTH. CRIT. CARE ) ( United Kingdom) 2001, 12/1 (25-33)  
CODEN: CCCAE ISSN: 0953-7112  
DOCUMENT TYPE: Journal ; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 51

The five basic principles behind the concept of the treatment of an established infection are as follows: (1) surveillance and diagnostic cultures to ensure identification of the micro-organism so that modification of the otherwise 'blind' treatment can be undertaken; (2)

immediate and adequate antibiotic treatment in order to sterilize the infected internal organs; (3) the source of potential pathogens causing the infection - whether endogenous or exogenous - requires elimination for both the recovery of the original infection and the prevention of relapses and/or superinfections. Selective decontamination of the digestive tract (SDD) aims at the eradication of internal sources of the oropharynx and gut in patients, whilst identification and eradication of the external sources outside the patients, using disposables and/or hygiene, are an integral part of the therapy of infection; (4) removal or replacement of invasive devices often contaminated with the potential pathogen is thought to contribute to the healing in curtailing the supply of micro-organisms; (5) surveillance samples are indispensable in evaluating the efficacy of this five component protocol. The treatment of practically all infections relies on these five basics, in particular lower airway and blood stream infections developing in the critically ill requiring intensive care including mechanical ventilation. Special attention is given in this chapter to the under-estimated problem of exogenous infections due to intensive care unit (ICU) associated bacteria without preceding carriage, and to the increasing problem of the serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). (c) 2001 Harcourt Publishers Ltd.

20/7/17 (Item 3 from file: 73)  
DIALOG(R)File 73:EMBASE  
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06928072 EMBASE No: 1997212551  
Therapy of severe visceral infections  
THERAPIE VON SCHWEREN VISZERALEN INFEKTIONEN  
Gabler-Sandberger E.  
Notfall Medizin ( NOTF. MED. ) (Germany) 1997, 23/5 (184)  
CODEN: NOMED ISSN: 0341-2903  
DOCUMENT TYPE: Journal; Note  
LANGUAGE: GERMAN

20/7/18 (Item 4 from file: 73)  
DIALOG(R)File 73:EMBASE  
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05470631 EMBASE No: 1993238730  
Taurolidine : In vitro activity against multiple- antibiotic resistant nosocomially significant clinical isolates of *staphylococcus aureus*, *enterococcus faecium*, and diverse enterobacteriaceae  
Traub W.; Leonhard B.; Bauer D.  
Inst fur Medizinische Mikrobiologie, Haus 43, D-66421 Homburg/Saar  
Germany  
Chemotherapy ( CHEMOTHERAPY ) (Switzerland) 1993, 39/5 (322-330)  
CODEN: CHTHB ISSN: 0009-3157  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Taurolidine at  $\leq 1,250$   $\mu\text{g/ml}$  killed all 37 isolates of multiple-antibiotic - resistant *Staphylococcus aureus* (n = 9), *Enterococcus faecium* (n = 17), and Enterobacteriaceae (n = 11). Timekill experiments disclosed that bovine serum (65% v/v) only marginally retarded the

bactericidal activity of 2,000 and 1,000 mug/ml of taurolidine against the various strains. Taurolidine at 2,000 mug/ml did not antagonize the bactericidal activity of 50% (v/v) fresh human serum against promptly and delayed serumsensitive test strains of Escherichia coli and Serratia marcescens. In the presence of 65% (v/v) of fresh defibrinated human blood from two donors, however, the bactericidal activity of this antimicrobial compound was delayed, i.e., manifested only following extended (overnight) incubation, against staphylococcal and enterococcal isolates, though less so in the case of Enterobacteriaceae. Taurolidine at 2,000 mug/ml killed ingested, i.e., intraphagocytic bacteria of human-serum-resistant S. marcescens strains CDC 06:H3 and P 016:H-.

20/7/19 (Item 5 from file: 73)  
DIALOG(R)File 73:EMBASE  
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05307599 EMBASE No: 1993075684  
Factors influencing the adhesion of uropathogens to the uroepithelium  
Reid G.; Bruce A.W.  
Research Services, SLB 328, University of Western Ontario, London, Ont.  
N6A 5B8 Canada  
Current Opinion in Urology ( CURR. OPIN. UROL. ) (United Kingdom) 1993,  
3/1 (21-24)  
CODEN: CUOUE ISSN: 0963-0643  
DOCUMENT TYPE: Journal; Review  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

20/7/20 (Item 6 from file: 73)  
DIALOG(R)File 73:EMBASE  
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01634630 EMBASE No: 1980129105  
Nebacetin(R) and taurolin as intra-operative disinfectant solutions in surgery of the locomotor system  
NEBACETIN(R) UND TAUROLIN ALS INTRAOPERATIVE SPULLOSUNGEN BEI EINGRIFFEN AM BEWEGUNGSAPPARAT  
Burri C.; Lob G.; Rudzki M.  
Abt. Unfallchir. Plastische Wiederherstellungschir., Univ. Ulm Germany  
Aktuelle Traumatologie ( AKTUEL. TRAUMATOL. ) (Germany) 1980, 10/2 (65-72)  
CODEN: AKTRA  
DOCUMENT TYPE: Journal  
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH

The anti-infective preventive action of intra-operative disinfection with physiological solution containing antibiotics, appears to be firmly established, judging from numerous publications. Since germs are showing a world-wide increasing resistance, the search for antibiotics which continue to be effective must be kept up, but alternative suggestions are equally necessary. Some publications have already been presented indicating that success similar to that previously obtained with antibiotics is possible by using disinfectants in the prophylaxis and treatment of infections. Hence, a comparative study was conducted using the non-absorbable broad-spectrum antibiotic Nebacetin(R) and the disinfectant taurolin in a 1% solution with a group of patients subjected to a total of

7699 major and minor surgical operations. Prospectively, early infections during the stay of the patient in the hospital, as well as disorder in the healing of the wound, were included. No significant difference was found in the number of infections and the rate of disorders in the healing of the wound. Indirectly, it is possible to conclude with the help of results from the literature that the disinfectant taurolin is suitable as an addition to intra-operative rinsing in the prophylaxis of infections.

20/7/21 (Item 7 from file: 73)  
DIALOG(R)File 73:EMBASE  
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01374980 EMBASE No: 1979095680  
Antibiotic therapy in acute peritonitis  
LE TRAITEMENT ANTIBIOTIQUE AU COURS DES PERITONITES AIGUES  
Gouin F.; Raybaud F.; Auffray J.P.; Viard L.  
Dept. Anesth. Reanim. Marseille-Sud, 13009 Marseille France  
Annales de l'Anesthesiologie Francaise ( ANN. ANESTHESIOLOG. FR. ) (France)  
1978, 19/11-12 (915-918)  
CODEN: AANFA  
DOCUMENT TYPE: Journal  
LANGUAGE: FRENCH SUMMARY LANGUAGE: ENGLISH  
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